Washington State Health Care Authority

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Health Technology Clinical Committee Public Meeting

January 18, 2019

Gregory Brown: We're bringing two topics today, sacroiliac joint fusion and peripheral nerve ablation for limb pain, and we will start with some program updates. We have two new members, and I am waiting for one of them to arrive before we let them introduce themselves, I think, before the next topics. So, Josh?

Josh Morse: Okay. Thank you, Dr. Brown. So, um, we give a brief program presentation. We do this at each meeting in the morning. So, my name is Josh Morse. I am the program director for the Health Technology Assessment Program at the Health Care Authority. As Dr. Brown said, there are two topics today, sacroiliac joint fusion in the morning, and in the afternoon peripheral nerve ablation for limb pain after the first topic. So, some meeting reminders, this meeting is being recorded. A transcript of the meeting will be made available on the HTA website following the meeting. When participating in discussions, please use your microphone and state your name, as this is very important for our transcriptionist who listens and then types up the meeting after we're done here. So, to provide public comment during today's meeting, please sign up if you're not pre-signed up outside the back doorway there.

So, a brief background about the Health Technology Assessment program. This program was created by the Washington State legislature in 2006 and signed into law by the governor at that time. It's designed to use objective evidence reports, and this panel of clinicians, to make coverage determinations for selected medical procedures and tests based on their evidence around safety, efficacy, effectiveness, and cost-effectiveness. Agencies that participate, so state agencies that participate in this program include the Health Care Authority that operates the Uniform Medical Plan, and the State Medicaid Program, or Apple Health, the Department of Labor and Industries operating worker's compensation program, and the Department of Corrections. The purpose of this program is to ensure that medical treatments, devices, and services, paid for with state healthcare dollars are safe and proven to work. This is a very high level view of how this process works. Topics can be nominated by anyone, including the

state agencies that manage these programs. Topic nominations are proposed. There is a review and a public input process. They are ultimately selected by the director of the Health Care Authority. Once selected and public comment periods are concluded, we develop a draft key questions and scoping document to determine how to address the policy questions through the evidence. These are then assigned to a contracted technology assessment center that produces a draft evidence report. The draft evidence report is released for public comment. It is then finalized and brought to this group in public meeting. This group reviews the report, hears comment from anyone who is interested in providing comment, and makes a draft coverage decision. At a subsequent meeting, the draft is reviewed and voted on to be final. Then, the agencies are charged to implement these decisions.

So, the calendar for the current year, let's see how far that goes. So, today's meeting, again the two topics for today. The next meeting with topics for review is May 17th where proton beam therapy will be rereviewed. The follow-up meeting for that is a conference call or webinar scheduled for July 11th to conclude the work from the May meeting. September is typically the time for the committee retreat, and we have not assigned a topic yet for the November 15th meeting.

So, people interested in participating in this process, we recommend you sign up at the Health Care Authority website, which is shown here on this slide. You can see all of the products that are produced and released for comment. You can sign up to receive our emails via our list serve program, and anyone may provide comment on proposed topics, key questions, draft and final reports, and draft decisions. The announcements for those go out through the list serve, again, where you can sign up for that on the Health Care Authority website. People are welcome to attend these meetings and provide comments directly to the clinical committee. Of course, anyone also may nominate health technologies for review by this group. There is a nomination form on our website. Thank you, very much. There is more information on our website, as shown there, and our program inbox is the state health technology assessment program, or shtap@hca.wa.gov. Thank you very much.

Gregory Brown: Okay. Thank you, Josh. So, next on our agenda is our previous meeting business. So, if we have our draft minutes from our November 16th, 2018, meeting. Any comments or changes for those minutes? Okay. Seeing none, I will ask that we...

Mika Sinanan: Second.

Gregory Brown: Second. Okay. Thank you. All in favor, aye.

Group: Aye.

Gregory Brown: Any opposed? None opposed. So, unanimous to pass those minutes. Then, the next issue is the draft findings for tumor treating fields, and those are listed here.

Sheila Rege: There were no public comments on that.

Gregory Brown: Okay. So, no public comments, so nothing to review there. Our decision there is not covered for newly diagnosed, recurrent, or for other cancers. So, does that appropriately reflect our discussion and findings at the time? Okay. So, then a motion for a final vote to approve those findings and decisions.

Josh Morse: I'm sorry to interrupt, but there's one typo on here. There's an extra parentheses, and we'll correct that.

Gregory Brown: Okay.

Josh Morse: In the first page of the decision, right there.

Gregory Brown: Okay. So, aside from the editorial correction of an extra closing paren, any other changes that we need to make? Okay.

Sheila Rege: Move to accept with the correction.

Gregory Brown: Okay. A second.

Laurie Mischley: I do.

Gregory Brown: Okay. So, all in favor of that say aye.

Group: Aye.

Gregory Brown: Any opposed? Okay. And I'm guessing, since we have two new members that weren't here, you're abstaining. So, I guess it was nine, or well, Seth is not here, so eight and two abstentions. Okay. And with that opportunity, we do have two new members. We will start with Jana Friedley. If you would like to introduce yourself and your background and new to our committee. Thank you for joining us.

Janna Friedly: Thank you for having me. I am Janna Friedly. I am a physician at the University of Washington in the department of rehabilitation medicine.

I've been there for about 15 years, and my clinical area of expertise is in amputation rehabilitation, but I also do comparative effectiveness, cost and outcomes research on musculoskeletal disorders and specifically low back pain.

Gregory Brown: Welcome. And Dr. Austin McMillin from Tacoma.

Austin McMillin: Good morning. I'm a chiropractor in Tacoma in fulltime practice. I've done quite a bit of work in the past as a technical advisor for the Health Care Authority and healthcare reform and working on issues for Labor and Industries and then also in legislative issues.

Gregory Brown: Welcome. Thanks for joining us. Okay. Should we go around the table and just brief introductions, or at least stating your names and position on the committee. Let's start with you, Laurie.

Laurie Mischley: My name is Laurie Mischley. I'm a naturopathic physician and epidemiology research.

Kevin Walsh: I'm Kevin Walsh. I'm a family medicine physician at a community health center in Ellensburg and a faculty on the family medicine residency there.

Tony Yen: I'm Tony Yen. I'm a hospitalist at Evergreen in Kirkland. I'm also the chief medical information officer for our organization. We just started our cardiology go live yesterday. That's why I'm a little bit tired today.

Chris Hearne: I'm Chris Hearne. I'm a nurse practitioner in post-acute care with Swedish.

John Bramhall: I'm John Bramhall. I'm an anesthesiologist. I work at Harborview, part of the University of Washington system.

Sheila Rege: I'm Sheila Rege. I am a radiologist oncologist in the Tri-Cities, also involved in organized medicine looking at outcomes and quality measures and stuff like that. So, this is a very interesting committee for me.

Gregory Brown: And also vice-chair of this committee. I'm Gregory Brown, and I already introduced myself. Josh has introduced himself. We have our expert today, Dr. Coner Kleweno.

Coner Kleweno: Yeah, my name is Coner Kleweno. I'm an orthopedic traumatologist at the University of Washington department of orthopedics sports medicine. I work almost exclusively at Harborview Medical Center. My practice is general orthopedic trauma with a focus on pelvic trauma.

Mika Sinanan: Hi, Mika Sinanan. I am a surgeon at the University based at Northwest and University of Washington Medical Center. I've been there 30 years, GI and general surgery, including minimally invasive, and I am on the executive committee for the Washington State Medical Association.

Gregory Brown: Thank you all for your time here today, and our two topics that we're going to review in advance for all your hard work. So, we've had our previous meeting business. We've had introduction of everybody, including our new members, and I think we are ready to start with our first topics.

Josh Morse: I'm sorry, one other... we have a PET determination to conclude. Yeah, I think if you... no, that's tumor treating... it should be the next one.

Gregory Brown: So, did it get... Okay. There it is. So, under the positron emission scans for lymphoma rereview, we had... our decision was nine to zero cover with conditions, and are there any... there was one public... there were some comments regarding advanced stage Hodgkins lymphoma needs an exception to the rules. A negative PET scan done two weeks after the fourth cycle of ABVD chemotherapy allows us to de-escalate chemotherapy and avoid toxicity. So, this should be an exception to waiting the three weeks for the completion of the chemotherapy cycle. So, was there any discussion around that change to the decision, or the conditions, I guess would be a better way to say that? No comments? Does everybody agree with that change?

Group: Mm-hmm.

Gregory Brown: Do we have specific wording that we're going to include that then in our decision?

Josh Morse: We do not have a draft for that.

Gregory Brown: Okay. We probably want that today here, then, don't we? I'm trying to see where the exact, the actual, where we stated the conditions. Okay. So, then, under the first bullet point, when used to assess the response to chemotherapy, scans should not be done any sooner than three weeks after completion of any chemotherapy cycle, except for advanced stage Hodgkin's lymphoma after four cycles of ABVD chemotherapy. Okay? Is that pretty straightforward? On our other decisions when we write them, we ask for a five or ten minute pause to kind of let us think about it. I think this is a fairly minor editorial comment. Does anybody feel we need a pause?

John Bramhall: Greg, what was the authority for that comment? I missed it.

Gregory Brown: Yeah. So, and that exception, it allows them to de-escalate sooner so they don't have to wait the three weeks.

Sheila Rege: And we can avoid radiation, so it makes us... so, we would just add a comma and except for advanced stage Hodgkins lymphoma after four cycles of ABVD chemotherapy. And I don't know if you say...

Josh Morse: Okay. So, I believe I have the edit. Can I... I'll read it back to you. This is for the first bullet. Is that correct?

Gregory Brown: Correct.

Josh Morse: Okay. So, the first bullet will instead read, when used to assess response to chemotherapy, scans should not be done any sooner than three weeks after completion of any chemotherapy cycle, except for advanced stage Hodgkin's lymphoma after four cycles of ABVD chemotherapy.

Sheila Rege: I would re-write. Mika, what do you think?

Mika Sinanan: It makes sense.

Sheila Rege: It's not quite [inaudible], but don't worry about it?

Gregory Brown: Okay. Everybody accept that? All in favor of accepting that change. Actually, I guess we need a motion first.

Mika Sinanan: Motion to approve the amendment.

Gregory Brown: And a second?

Sheila Rege: Second.

Gregory Brown: Any further discussion? Okay. All in favor, say aye.

Group: Aye.

Gregory Brown: Any opposed?

Josh Morse: Thank you.

Gregory Brown: Okay. We're gonna try one more time. So, we are now ready to start sacroiliac joint fusion discussion. So, our Health Care Authority presentation.

Emily Transue: So, hello and welcome. I'm Emily Transue, associate medical director at the Health Care Authority here to speak today about sacroiliac joint fusion. I'll apologize in advance. I have a cold and I'm on cold medications. So, perhaps not entirely [inaudible].

Background on this topic, of course it would be hard to overstate the importance of low back pain in terms of burden of disease and disability. Estimate 4 to 25% prevalence in adults at any given time. This is really one of the biggest drivers of healthcare utilization and disability in the country. The SI joint has been implicated as the pain source for many patients. Some studies project that 10 to 30% of low back pain may derive from the SI joint. In this context, of course, there is a very strong desire, by both patients and providers, for effective treatments. On the other hand, I think it's important to context that we do see a history of procedural overuse and would call out spinal fusion here as an example with high costs and harm to patients in the low back pain arena. This really highlights the needs for rigor in assessing the evidence for treatment options.

Sacroiliac joint fusion is built on the theory that pain in the sacroiliac region may be related to instability in the sacroiliac joint and that mechanically stabilizing the joint with a screw or specialized device would then decrease the pain. Candidates for this procedure include surgically-naïve patients, but this is also done in a significant number of patients who have sacroiliac pain after lumbar fusion, and the theory here is that decreasing motion in the lumbar spine can put increased pressure onto the sacroiliac joints. A variety of devices, as well as surgical screws have been used, but the control trial data is almost exclusively about a specific device called iFuse, which consists of two to four triangular rods that are placed across the joint via minimally-invasive surgery. The data vender is going to discuss the whole spectrum of evidence around fusion, but I'm really gonna focus on this device, since it is where the highest quality evidence is, which I expect will ultimately drive your decision.

Designated CPT and HCPCS codes around this particular procedure, 27279 is for the minimally-invasive procedure, and 27280 for the open procedure.

Current agency state policy in PEBB and UMP, this is covered and prior authorization requirement will be in effect in February of this year. Prior authorization is also required for the open procedure. In Medicaid, this is not covered for both open and minimally invasive. Labor and Industries covers in the setting of substantial trauma with documented sacroiliac joint disruption as documented on MRI.

Current utilization, looking back at 2014 to 2017, we had fewer than 11 procedures that were paid for by state-covered programs, which is our threshold for public reporting. So, I can't give you an exact number, but not many of these are being paid for in state programs.

Because of that very small number, there is a wide range of costs, and they're a little hard to interpret. So, I'm just going to give you the median billed charges for minimally invasive surgery procedures on this, around $19,000, and the median allowed amount $10,500, just to give you a ballpark on payment for these.

Agency medical director concerns around these procedures are high for safety, and we'll talk more about that in a minute, high for efficacy, and high for cost. So, a lot of concerns in all areas on this.

Key questions, and we'll go over kinda quickly, since this is the template for all Health Technology Clinical Committee evidence reviews with the evidence of efficacy and effectiveness for this procedure compared to alternatives. What direct harms might it cause? Do the outcomes vary by indication and patient characteristics? And then, finally, what is the cost-effectiveness and other economic implications?

For context around these devices, I think it's important to know that all of these devices were approved using 510k approval, which is to say substantial equivalence to other treatments on the market. So, none of these have gone through pre-market approval studies.

Some of the limitations around the data that you'll see include that there really is not a diagnostic gold standard for this condition, including criteria in the trials vary. Typically, they include a combination of physical examination tests. There are a number of provocative physical examination tests for this procedure. Frequently, a positive response on three out of five of those is required. Reduction of pain with an SI anesthetic injection is also a typical requirement for entry. And that can vary 50%, 75%, 80% reduction, and some require imaging guidance for those injections and others not. Given the lack of a single gold standard, I want to call out that there are some studies showing poor reliability of the physical exams. So, a study looking at pooled parameters of inter-rater reliability for physical exams in this condition showed a low value at 0.2. So, some issues around physical examination reliability here. Another concern in terms of entry criteria, given that sacroiliac joint anesthetic injection response is typically a requirement for entry into studies or coverage, there was a study showing no relationship between the level of response that people had to those injections and their six to twelve-month

pain and disability scores after fusion. So, some question about whether taking anesthetic correlates to people's long-term outcomes.

Other concerns that we had around the data, every study evaluated, and the vendor will present this in more detail, except for the cost studies, showed either serious or very serious risk of bias. These clustered around a number of areas. One was on the comparator. So, conservative management is typically the comparator, but was defined at provider's discretion, and an evidence-based multidisciplinary pain management program was not used as the comparator. Additionally, and I think this is the single biggest area of concern for the agency medical directors, there was a lack of blinding. So, no sham studies were performed. And patients, providers, and evaluators were all unblended to the study arm. We think this is a particularly important consideration, since these are subjective outcomes. So, potentially particularly vulnerable to the placebo effect. Controls, I wanted to talk about this, too. Controlled trials, but most of the available benefit comes from uncontrolled studies. And in terms of funding, all of the trials were funded by the device manufacturer.

I'm going to focus on effectiveness on the key studies. These are two randomized control trials, both of which compare iFuse to conservative management. Both of these studies are ongoing prospective open-label multicenter randomized controlled trials. These are unblinded, as mentioned, so no independent assessment of outcome, manufacturer funded, crossovers were allowed from the non-surgical group to the surgical group after six months, and conservative management was at provider discretion and not standardized. We're going to talk about each of these trials, and then I'll present you the results together.

So, the Insite Trial, done in 2015 in the U.S. comparing iFuse to non-operative treatment. This was done at 19 centers and involved 148 patients, about 38% of those having had prior lumbar fusion. Diagnostic criteria were history of sacroiliac joint pain, three out of five provocative jointing findings, and a 50% reduction in pain with block. Crossover was allowed at six months and by two years, 88.6% of the non-surgical patients had crossed over. So, ultimately 142 of the 148 patients in the trial got surgery. So, we had a little comparative result after six months. Conservative management typically excluded CBT-based treatments, as their assessment was that these were unstandardizable, impractical, and unrepresentative of modern U.S. healthcare. So, CBT as part of pain control.

The iMIA trial, 2017 at multiple European sites, again comparing iFuse to non-operative treatment. This involved nine centers, 101 patients, about

35% had a prior lumbar fusion. Diagnostic criteria, the Fortin finger test. Essentially, ask the patient to point with one finger to where the pain is, and if they're within a centimeter of the sacroiliac joint, it's positive. Again, three out of five provocative joint findings, 50% reduction in pain block. Crossover, again, allowed at six months, a little bit lower rate of crossover here but still substantial.

What did these studies show? So, here we have the results. Insite is on the top with one, three, and six month results. And the iMIA below with one, three, six months, and one year results. I don't think there's any question here that [inaudible] impressive magnitude of facts. So, starting with pain assessment with visual analog scale. So, this is a 100-point scale with a minimally clinically important difference coming in at around 10. We're seeing results in the 30 up to 40, increasing in the course of one to six months, decreasing a little bit at one year but still highly significant. Looking at the disability scores, again, Oswestry Disability Index. Again, here, minimally clinically important difference of around 10, and we're seeing quite large numbers, 13, 19, six months we have the 25, and the iMIA trial preserving that out to a year. Quality of life [inaudible] trials using the short form health survey 36 and the New York Pain Trial with [inaudible]. Again, very significant results in both physical and mental. The Insite trial looks at opioid abuse and found that in the surgical group, there was a decrease at six months on the percentage of patients who were taking opioids, had decreased in that group from baseline by 9%, and in the group who did not receive surgery had increased by 7.5%. So, that's the percentage of patients who were taking opioids. I don't know that that was preserved out to two years. At two years, the percentage of patients taking opioids had decreased from 70% at baseline down to 50%. We don't have a comparator there, because we don't have a significant number of patients who didn't, but that's okay. So, really no questions about [inaudible] of results. I think probably Dr. Franklin used the word miraculous. You know, Dr. Franklin is the big believer in miracles. I think the question is really around how much confidence we can have in these results, given the high concerns that were discussed earlier.

Moving on to safety. There were not common protocols for data assessment or standardized definitions. So, this is somewhat hard to assess from the trial data. Range of adverse events given for iFuse ranging from zero to 30. It was a study based on CPT codes after minimally invasive sacroiliac joint fusion, which found a 13% complication rate at 90 days, and that was pretty stable after six months. The most common postoperative complaints are neuritis or radiculitis. Post market surveillance data showed 2.8% of patients having revisions over a median of four years.

Again, thinking about safety, what does it, what does it look like when things don't go well? This is a sample that was taken out of the FDA Maude adverse events database from November. I tried to update this last night. Actually, but [inaudible] related to the governor. So, pulling out just a sample in those cases, so patients who had surgery with three implants didn't have pain relief but subsequently had all three implants removed using chisel, as they were solidly fixed in bone. Other patients who had increased pain six weeks after the procedure, CT showed a cranially-positioned implant that was impinging on the neural foramen, had a revision procedure where the implant was removed using osteotomes [inaudible] solidly fixed in bone. We also had, yesterday, an Labor and Industries case came to Dr. Franklin's attention, a 42-year-old patient who underwent surgery in 2015, and that was with the Rialta [inaudible] iFuse, subsequently had a revision and an L5-S1 fusion, has ongoing low back, right leg pain weakness, urinary incontinence. So, [inaudible] but when things do go badly, it can be pretty significant, and this is definitely a procedure that is not easily reversed.

Differential impacts by population, we really don't have any data to differentiate how different people will respond to this. Specifically L&I patients were left out of many of the studies.

Cost-effectiveness, low quality of evidence, but a couple of studies, the Ackerman study listed iFuse versus non-operative patients in a commercial population and found that the iFuse costs $15,000 more over the first three years. That was decreased to $6000 more than conservative treatment over five years. Looking at a Medicare population, that same group found a cost savings of $3,300 over the course of a lifetime, because of decreased expenses in conservative treatment. There's one study on cost-effectiveness, which estimated $13,000 per QALY and a breakeven point at 13 years. So, below the threshold, certainly, of what we could typically consider acceptable.

Coverage comparison, Medicare has no national coverage determination. Local coverage decision I won't go through in too much detail but includes failing at six months of non-operative treatment, many of the physical findings that we discussed, absence of generalized pain behavior or generalized pain disorders, and 75% reduction of pain with imaging-guided anesthetic.

Local coverage comparisons in our market, AETNA, CIGNA, Kaiser, and Premera in the Washington market cover only for instability associated with major trauma, such as pelvic ring fracture or as adjunctive therapy for infection versus malignancy, but do not cover for mechanical low back

pain, sacroiliac joint syndrome, or radiculopathy. I would call out the national Premera decision, which is using Medicare, it actually does cover for some of the conditions that we've talked about earlier. Regence covers when ADLs are impacted and then, again, a similar list we have seen earlier, six months on non-operative treatment, pain reduction with anesthetic. They require a steroid injection and, again, a lack of a generalized pain syndrome.

Guidelines, the NICE guidelines consider the current evidence is adequate to support this procedure but should only be done by experienced surgeons. The AIM Specialty Health, actually, let me put it out there that we have heard reports of these being done by people who are not orthopedics or neurosurgeons. So, I think the [inaudible] confuses [inaudible]. AIM Specialty guidelines say it may be considered medically necessary when pain interferes with function. Again, many had the same criteria that we discussed before.

We had a lot of discussion about this among the medical director group, and these are the recommendations we would like to present to you. So, our recommendation is that this be covered with conditions. Specifically, that sacroiliac joint fusion with either iFuse or open fusion, it's medically necessary when all of the following are met: Imaging studies demonstrate localized sacroiliac joint pathology and it occurs in the setting of posttraumatic injury to the SI joint, such as pelvic ring fracture with radiographic evidence of joint disruption or as an adjunctive treatment for joint infection, perhaps a sacral tumor or when performed as part of a multi-segmental long fusion for correction of spinal deformity.

And that it is not covered for any other indication but be considered experimental and investigational, and that would include mechanical low back pain, SI joint syndrome, degeneration, and radicular pain syndrome. The rationale for the recommendation is really that the evidence for efficacy in these conditions is based on un-blinded manufacturer-funded trials with a high risk of bias and a lack of effective data, and that serious adverse events may be under-reported. Any questions?

John Bramhall: I was going to ask you, you mentioned a pretty small number of these cases that are funded from public funds. Is there a [inaudible] larger number of people who get this procedure through commercial coverage? I'm really sort of asking, what's the current state of play? How many, how many get this procedure at the moment?

Emily Transue: Our expert may be able to speak to that better. I think it's an evolving field. Coverage is very variable across commercial markets. So, I don't know what the total numbers look like.

Coner Kleweno: No. I think that'd be great data to have. I am not aware of the current prevalence or incidence for these procedures in the commercial market.

Emily Transue: I think we are seeing an increasing number of requests, which is one of the reasons that we wanted to bring it up before the group.

Mika Sinanan: I wanted to be clear that patients who are having this procedure virtually all have had a block. Is that right?

Emily Transue: Yes.

Mika Sinanan: All or virtually all? I mean, is it just very common, or is it always done following a block? Do you know?

Emily Transue: A block is part of the inclusion criteria in all of the trials reviewed and in all of the coverage criteria that we've looked at. So, I would assume that's all, unless anybody's rogue and not [inaudible].

Mika Sinanan: Thank you.

Laurie Mischley: One of the limitations that you called out was the lack of defining what conservative treatment was, but you're not making any recommendations about defining conservative treatment in here. Is there a reason that you chose to avoid that?

Emily Transue: Yeah. Essentially, we are recommending that this not be covered for people that would be applicable for. I don't think there's any controversy that when the patient has had a pelvic fracture and had a clearly dysfunctional joint of similar cause that they ought to have the procedure. The question is really whether people who are in that kind of mechanical low back pain should have it. Since we're...

Austin McMillin: Speaking of the list of conditions that you recommend that this be used in, are these fairly uncontroversial, or are these, are these found to be pretty effective?

Emily Transue: Yeah. I think these are, these are uncontroversial.

Austin McMillin: Okay.

Emily Transue: These are patients who clearly need to have an intervention and this seems to be a good intervention as [inaudible] clinical controversy lies.

Coner Kleweno: Coner Kleweno here. I had a question on one of your last comments from the previous slide. You said imaging demonstrating local SI joint pathology, were there any details provided on that? Was it x-ray or CT scan or how is that defined, just a question?

Emily Transue: A great question. It was defined differently in different places. The Labor and Industries criteria require MRI, and this certainly could be something that the group could decide to [inaudible].

Chris Hearne: I'm sorry, to that point, if you have somebody [inaudible] about how you might define joint disruption from the MRI in somebody that's had trauma, that would be helpful, I think.

Coner Kleweno: Well, a couple different things. So, one is a disruption. That's in the setting of trauma. So, that's very clear, typically, and defined by a CT scan. Now, there is, in that setting, still debate as to how much instability or how much disruption requires an acute treatment. And that's something that are trying to determine on the trauma level. Where this procedure is typically used is in the chronic, if someone has chronic issues and pain as opposed to an acute car crash, etc. The reason I asked the question is, there's a relatively nice study based on CT scan imaging of asymptomatic patients, so patients who were admitted to the hospital and got a CT scan for rule out trauma or abdominal pain. And a huge amount of patients had evidence on CT scan of SI joint abnormality, whether that was degeneration of the SI joint or arthritic disease of the SI joint. And the incidence of that was quite high, and all of these patients were asymptomatic, per their SI joint. So, that's why I was curious as to what you meant by the imaging defining pathology to the SI joint.

Emily Transue: That's a great question. Bring that slide back up. So, think that's sort of where the, that would only be considered in the setting of posttraumatic injury or one of these other pathologies, not just an association with pain.

Gregory Brown: [inaudible], did you get your answer, your question answered that way?

Female: Oh, yeah.

Gregory Brown: Okay. Alright. I just had one other quick... the two RCT's presented, did either of them break them down by subgroup, as to diagnosis for the indication for the procedure? Was there a posttraumatic subgroup versus a?

Emily Transue: So, none of these were posttraumatic. They were all related to sacroiliac joint syndrome scenario. They didn't differentiate between the post-lumbar fusion group and the non-post-lumbar fusion group, or other subgroups.

Gregory Brown: Okay. I'll save other questions for our report from the contractor. Any other questions?

Janna Friedly: I just had a quick follow-up question. In the European study, they also included a fairly substantial peripartum or, you know, pregnancy-related SI joint as dysfunctional, even though that's not sort of called out. I assume that falls into the, into the cate-, you're, you're considering that in the, in the mechanical low back pain...

Emily Transue: Yeah.

Janna Friedly: ...category.

Emily Transue: That's correct.

Coner Kleweno: Alright. Just to specify, you're saying that's not included in posttraumatic injury, the postpartum?

Emily Transue: Correct. And we could call that out in a revision if you go in that direction.

Gregory Brown: And just for clarity, if I may, just so we're all on the same page, my understanding of postpartum causes the, that the actions of relaxin at the time of delivery can cause stretching or strains to the sacroiliac ligaments and later than during SI joint dysfunction in a postpartum female. Is that, the pathophysiology that is at least proposed is that everybody on the same page?

Coner Kleweno: I would say that maybe an average case, there are cases where there is an acute disruption of ligamentous stability in the setting of a vaginal delivery or around that process. So, I think those are two different clinical scenarios where there is a normal relaxing, and then there are cases of, you know, failure of the ligament to stability, relative failure and two different pathophysiologies for how much stability is at that time.

Emily Transue: Are those distinguished?

Coner Kleweno: I would say it's a spectrum; however, when there is an acute failure, it is pretty obvious. There is a substantial diastasis of the pubic symphysis on

imaging if that's obtained, and there is often associated with a symptomatic... a constellation of symptoms is different than normal peripartum vaginal delivery.

Emily Transue: And it is your clinical belief that that should be considered a posttraumatic injury versus mechanical sort of in the different category or?

Coner Kleweno: I think it'd be further discussion regarding that would be required, but there is definitely a different clinical scenario of a partial failure of ligamentous stability, as opposed to just stretching of the ligaments.

Gregory Brown: Okay. We are actually a few minutes past our scheduled open public comments. So, thank you very much for the presentation. Can we open the microphone for... okay? We had nobody sign up late.

Josh Morse: No. We do have a scheduled.

Gregory Brown: Oh, we do? Okay. Should we go with that first, then? David?

David Polly: Yes.

Gregory Brown: Hi, David. It's Greg Brown.

David Polly: Hi Greg. Hopefully you guys can hear me, and you have my slide deck?

Gregory Brown: We hear you well, and we are bringing up the slide deck.

David Polly: My apologies. I had surgery last Friday, and I could not be there in person.

Gregory Brown: I hope you're doing well.

David Polly: Thank you. My name is David Polly. I'm the professor in chief of spine surgery at the University of Minnesota. I am also representing the American Academy of Orthopedic Surgeons, the American Association of Neurological Surgeons and Congress of Neurological Surgeons, International Society for Advancement of Spine Surgery, and the Washington State Association of Neurological Surgeons. All of these societies asked me to provide these comments to you. In addition, I was asked by your committee to be a reviewer of the initial draft report. My disclosures are that I have Springer textbook royalties. I was an investigator on the Insite clinical trial, but I received no financial support from the industry of any kind, since 2010.

My summary comments are that this review was a rigorous methodology of existing published peer view data. The conclusions in the report, from RTI, are supported by the data. The highest quality clinical data are about the trans-iliac-trans-sacral approaching using the triangular titanium rods, as mentioned by the previous speaker, the iFuse implants. It is unclear if this is generalizable to other devices or approaches, and that was a comment specifically from the double ANS/CNS reviewer who wanted to see about making it more generalizable. I would say that the review, as reported, reports the data.

The criteria for surgical treatment specifically, we agree with the positive finger Fortin, Fortin finger test, positive three out of five physical examination maneuvers constituting a positive physical examination, and then greater than 50% pain relief with an image-guided injection, as non-image guided injections often are not into the joint.

There are several concerns that we would like to express. The data is good for the patients who meet the inclusion criteria for the RCT's, but there are patients who do not meet those specific criteria who may also benefit. I found it interesting, the comment about cognitive behavioral therapy, as I am personally unaware of any data about CBT, as it addresses the SI joint specifically. No argument about non-specific low back pain or generalized pain syndromes, but I'm not aware of it specifically for the SI joint. So, the data to support continued non-surgical management of patients who have failed an initial course of physical therapy or non-operative treatment is of lower quality than the surgical data is. So, the question to the technology assessment committee here is, what treatment will be allowed for these patients, and the suggestion is that perhaps Washington State might consider a strategy of coverage with evidence development to generate meaningful real world data on this cohort, the cohort who do not meet the clinical trial inclusion criteria. And I would be happy to answer any questions.

Gregory Brown: Thank you, Dr. Polly. Any questions from the committee?

Janna Friedly: When you mentioned there are patients who don't meet specific criteria who also may benefit, can you be a little bit more specific about who those patients are and what, why they didn't meet inclusion criteria?

Davi Polly: Sure. So, the clinical trials are based off of primarily the Laslett information, and there are several review articles suggesting that three out of five physical examination maneuvers has an 85% positive predictive value for response to an image-guided injection. What we don't have data about is, what about two out of five, or one out of five, and what is their

response rate. Then, whether or not they respond, as none of these patients were included in either the Insite or the iMIA clinical trial. So, we don't know if they will be responders or not. The other piece that is a bit of a challenge has to do with the injection criteria, specifically, the injection has to be reasonably well done. Getting into the SI joint is not trivial, and it only holds about 2 cc of volume. Is there is extravasation of the contrast and the injectate out the front of the joint, that's an indication that the anterior joint capsule has been ripped. So, that makes it more difficult to interpret the injection response. So, you could have a physical examination positive patient who has an incompetent anterior capsule with extravasation of the contrast who may get a variable injection response.

Mika Sinanan: Thank you for that explanation. You pointed out that the clinical criteria are particularly helpful in selecting patients who respond to the injection, or who have a high response rate to image-guided injection with the caveat that you said at the end. So, the clinical responses and the injection are not independent predictors of a benefit. The clinical criteria really are predictors of whether somebody responds to the injection, and the injection is then used as a basis to determine whether a patient would benefit from a minimally-invasive approach to fusion. Is that a correct way to think about this?

David Polly: Well, what I would say in response to that is that the clinical trial data, the inclusion criteria includes failed non-operative management, three out of five positive physical examination maneuvers, and then at least a 50% response to the injection. We, we don't know... we don't have RCT data about people who are outside of that category, and the previous comment about the injection response I found interesting, because there's been some debate about the threshold for that response, and I think I heard that comment made earlier. So, then I'm the one who actually did that study. The North American Spine Society recommended a threshold of a 75% response, and then asking them where that came from, it was unclear to me. So, we did a study looking at the patients who had surgery and used our reference standard as those who responded to surgery and looked at those who had a 50 to 75% response rate to injection versus those who had a 75% to 100% response rate, and we found no difference in positive surgical outcomes between those response rates in the injections. I cannot conjecture or comment on those who didn't respond to the injection, whether or not the physical examination would have predicted a surgical outcome, as those patients were not eligible for enrollment in the clinical trial.

Mika Sinanan: We've heard that the patients who are selected for this are those who have a 50% or higher response rate to the injection, plus the clinical criteria.

David Polly: Correct.

Mika Sinanan: Right, but we also heard that there is a complete lack of correlation between their benefit at six and twelve months to the injection. So, the injections are being used to drive the decision for doing the implant, but have no correlation to whether or not there's a pain benefit. Is that correct?

David Polly: Well, no. I would not characterize it that way at all. I would characterize it as, there is, for patients who have the physical examination that's positive and a confirmatory injection, those patients have the response rates from the clinical trial, both clinical trials, demonstrating a high response rate to outcomes. What the study showed is that a high injection response and a low injection response didn't differentially prognosticate.

Mika Sinanan: Didn't prognosticate the benefit?

David Polly: Correct.

Mika Sinanan: For fusion? Okay.

David Polly: For high responders versus low responders, but all of the people who got the injection and went on to surgery, there was a, depending on your definition, 85% success rate of the surgical treatment.

Mika Sinanan: Some response but not necessarily high or low?

David Polly: Well, so I think the injection doesn't prognosticate a better or worse outcome if they get a 50% response. So, I think that's the threshold criteria that the literature suggests, as people who are candidates for the surgery, a better than 50% response rate does not predict a higher response rate of outcome from the surgical intervention.

Mika Sinanan: Thank you. And then, just one follow-up question. Is it your understanding that the criteria that have been, uh, quoted in the randomized trials are, in fact, the criteria that are being used clinically now?

David Polly: Yes, and that varies a little bit from payer to payer. And in Minnesota, a number of payers have utilized those criteria, and some have utilized the NASS criteria, and some have utilized the ISASS criteria. I agree with the RTI report for the surgical criteria, which were listed on my slide #4, which

they've summarized as a positive Fortin finger test, positive three out of five physical examination maneuvers, and a 50% or greater response with injection. I think those are the appropriate criteria and that the treatment of patients who do not have those criteria would be, in my mind, something that would be appropriate for coverage with evidence development rather than as a positive coverage determination of knowing that it works.

Mika Sinanan: Thank you.

Gregory Brown: Any more questions? Thank you very much, Dr. Polly, and we wish you a speedy recovery.

David Polly: Thank you, Greg. I appreciate it, sir.

Gregory Brown: Have a good day. Okay. We have nobody else signed up for presentation here. Can we open the mic for anybody that's calling in? We have? Okay. This is Greg Brown. I'm Chair of the Health Technology Clinical Committee, and we are reviewing sacroiliac joint fusion as our topic this morning, and we are wondering if there's anybody on the phone that would like to make a public comment? Okay. Not hearing any responses, we have no other public comments from the phone. So, I think we are ready for our report. Thank you.

Leila Kahwati: Hi, everyone. While the slides are getting loaded, I'll just introduce myself. I am Leila Kahwati. I am the lead investigator on the evidence review that I'll be presenting today on behalf of the RTI University of North Carolina Evidence-Based Practice Center. I am joined by my colleague, Dr. Cindy Feltner, in the back who was a co-investigator on this work, and we're happy to be here today.

So, this is just a brief overview of today's presentation. It's fairly standard. We will start with little bit of background, talk about the methods for the review, spend most of the time on the results, and then finally some discussion, such as limitations and implications.

So, you've already heard a bit about this topic. So, I might speed up in certain places where data have been covered, but we'll start with a little bit of background. So, sacroiliac, or I'll just refer to it as SI joint pain for timing, is thought to be the primary source of pain for approximately 10 to 30% of patients with mechanical low back pain. This data is based on 18 studies of patients with mechanical lower back pain that utilize controlled comparative local anesthetic blocks. Pain typically originates from either one or both surfaces of the joint, but it's important to note that the entire

SI joint complex, including the capsule, the ligaments and subchondral [inaudible] contain pain receptors. The clinical presentation of pain varies, but a typical pattern is pain over the SI joint region and extending a little bit into the buttock and into the posterolateral thigh.

As far as the etiology of the chronic SI joint pain, it's thought to be degenerative, sacroiliitis or joint dysfunction [inaudible] and location. Several predisposing factors for chronic SI joint pain have been identified in an epidemiologic stud and they're listed here on the screen, and you'll note that what they have in common across these sectors is that there is some alteration of the biomechanics at the SI joint, which then maybe goes into joint dysfunction and the degenerative process, leading to pain.

So, we've already touched on a little bit of the challenges related to diagnosis. So, for the purpose of this evidence review, I want to just make sure everybody is on the same page. That we're really talking about chronic SI joint pain. We're not talking about trauma. We're not talking about key injuries, because that's not really where the decision [inaudible] is. So, we're really focused here on chronic SI joint pain. So, the diagnosis of chronic SI joint is challenging, as you've heard, because there really is no universally accepted gold standard for diagnosis. Part of this review, we saw evidence for two contextual questions related to the accuracy of diagnosis and frequency of diagnostic testing and usual practice. So, guidelines and experts recommend a combination of an appropriate history confirmed by one or more physical examination, provocation, [inaudible] occurred, followed by a diagnostic SI joint injection with anesthetic to see if pain is relieved after injection; however, recommendations are meant to confirm the suspected diagnosis with SI joint injections do vary. Most recommend diagnostic SI joint injections for those with chronic non-radicular back pain, pain that's in the SI joint region, and who have three or more provocative [inaudible] joint pain, and an otherwise negative [inaudible] and lumbar examination, which could include imaging to rule out other etiologies of pain.

A few words about the physical examination. We've heard about the Fortin Finger test. This is a test in which the patient is asked to put a finger over the area where they feel the most pain, and if they put their finger over this red oval area, which is directly over the SI joint, this area is named the Fortin area after the author who created a pain referral map based on provocative injection. So, if they point to that region, there's a higher likelihood that the etiology of the pain is from that [inaudible] SI joint. Other provocative physical examination are listed on the slide and the image here at the bottom shows one of those maneuvers, the Gaenslen

maneuver, which applies torsional stress in either the supine or the lateral position.

Gregory Brown: Actually, before you move, so the criteria were three of five, and there are six tests listed. Is there...

Leila Kahwati: I think there are probably even more than six, but I think these are the most common, but I think it's... the more you have... it's the principle. I don't know that there's anything magic about three or five versus four or six, but it... the accumulation of evidence that there might be something there. I don't know if our clinical expert can comment on that.

Coner Kleweno: Just it's, uh, you know, from a generic statistical standpoint, if you put a threshold and then increase the denominator, you're going to increase the numerator at some point, just by statistical probability. So, I think it's... just be cautious about quoting three out of five. We have no individual affect size of each of those tests, and as we saw in some of our other presentation that was six [inaudible].

Mika Sinanan: Followup question, as well. We've seen pictures, it seems that this appears to be more unilateral than bilateral or, is it bilateral?

Leila Kahwati: So, it can be bilateral, and there are, in the [inaudible] that we'll talk about in a little bit, there were patients with bilateral pain who received bilateral procedures, but it's the minority of [inaudible].

Gregory Brown: I guess my question is, is I thought the state recommendation was three out of five positive provocative tests. So, we need to clarify which of those five tests that we're gonna use, if that's going to be our criteria, I guess is my question. Anyway, we can do that in the discussion.

Leila Kahwati: Okay. So, a few words about diagnostic SI joint injection, which is what we've already heard a little bit about. So, it's the current reference standard for diagnosis. We don't use the term gold standard to refer to it, because it's likely an imperfect standard for diagnosis. So, we really couldn't find any data to quantify the magnitude of imperfection, but that would require to have a gold standard in order to do that. So, the injection should be under imaging guidance, as you heard from Dr. Polly, to insure intraarticular placement of a consistent volume of injectate, and to monitor for extravasation, as you heard. However, studies that had used diagnostic injections estimate the prevalence of SI joint pain have varied in the volume of injectate use, which could influence those prevalence estimates. Further, the amount of pain reduction, as we had talked about, recorded for a positive test, you could say, also varies. Some use a lower

threshold of 50%, some may use a higher threshold, up to 80%; however, as we just heard a lot of conversation about it, the actual threshold... once you reach sort of that 50% threshold, using a higher threshold, it may... it doesn't actually decrease the prevalence of SI joint pain by that much. So, there is some difference in prevalence, if you vary that threshold, but it's not as much as you might think. Some have argued using double or confirmatory block also helps confirm the diagnosis by reducing the prevalence of false-positive rates, just based on a single [inaudible]. We did not identify any studies that provided data from placebo [inaudible] injections to quantify the magnitude of a possible placebo effect from the injection, as well.

So, you already heard this data from Dr. Polly, but I'll just briefly mention it. So, in a pooled analysis of about 320 subjects from this RCT of SI joint fusion that were diagnosed as part of the enrollment criteria, there was a confirm [inaudible], as well, required 50% reduction of pain at 30 or 60 minutes after the injection, and the improvement in pain and disability after fusion was independent of the degree of improvement after block. So, what that means is the people who have a 50% reduction in pain after the block had just the same outcomes after fusion, in terms of effective outcomes, as people who had 70% or higher reduction after block. So, it's not that there is no association between improvement and fusion outcomes. It's that once you sort of reach a threshold of about 50%, it normally doesn't matter how much relief you got from the injection. You're going to have the same outcomes after surgery.

So, this is from data on the accuracy of various physical examination [inaudible] diagnose SI joint pain. Again, this is a reference standard here. The diagnostic SI joint injection, and these studies did vary, in that the [inaudible] required after a positive test, between 50 and 80%. So, that's why the estimate was pretty heterogeneous. As you can see, the sensitivity and specificity of these physical examination elements vary by test, and no single test of these that were evaluated had both a high sensitivity and a high specificity. So, you'll note that a combination of three or more positive tests has the higher specificity. So, if somebody's negative on three or more tests, it has a reasonable specificity of ruling out SI joint pain.

Mika Sinanan: Sorry, just to be clear, for ruling out lack of benefit or reduction of pain with a block? That's what it shows?

Leila Kahwati: Correct. Yes.

Mika Sinanan: You're inferring that that means that the SI joint is not the source?

Leila Kahwati: Correct.

Mika Sinanan: Okay.

Leila Kahwati: For the second contextual question, we sought out evidence to find out what are people actually doing in usual practice to diagnose this condition, and we really couldn't find any data describing typical patterns in clinical practice, such as surveys of providers or direct observation of care. So, I don't know if perhaps our clinical expert has anything to comment on what people are doing in usual practice to diagnose this, or if people are really following sort of the algorithm of doing a diagnostic injection.

Coner Kleweno: A comment on that, I think the physical examination can be quite variable, and the practices are quite variable. I think, as in all of medicine, there is a stark difference in physical examination for discovery, when you are trying to diagnose with a... amongst a list of differentials versus a confirmatory physical examination where you are collecting evidence to support a sort of preconceived diagnosis. So, that should be very clearly understood.

Leila Kahwati: Okay. So, moving on to SI joint pain management. So, surgical treatment to address SI joint pain is portrayed in the literature as a definitive treatment for SI joint pain by reducing excess motion at the joint. So, fusion is typically reversed for patients who do not respond to less invasive treatments, several of which are listed here on the slide at the top. So, SI joint fusion can be done via an open procedure, which allows for direct visualization of the joint. Alternatively, it can be done with minimally-invasive procedures using smaller incisions and under imaging guidance. So, according to practitioners, minimally-invasive approaches result in shorter interoperative times, less bleeding, and shorter hospital length of stay. Lastly, the percent of SI joint fusions performed using minimally-invasive techniques increased from 39% in 2009 to 88% in 2012, which is the most recent year for which we could find data, and this was based on surveys of members of the International Society for the Advancement of Spine Surgery, and the Society for Minimally Invasive Surgery. So, clearly, perhaps a biased sample, but it does speak to sort of increased prevalence and shift perhaps away from open fusion to minimally-invasive, even for this particular condition, chronic SI joint pain.

So, numerous proprietary surgical systems for sacroiliac joint fusion exist. Most are designed for minimally-invasive procedures. The systems typically consist of two or three specialized implants or screws that are deployed under imaging guidance to expand the joint for immediate

fixation, but they have specialized designs and specialized coating to promote bone growth onto and into the sphere where the implants. An example that we've talked about here is the iFuse implant system. There is a picture here at the top. These are triangular shaped titanium coated roads that have a specialized coating to promote bone growth, and they get deployed under imaging guidance to expand the joint. The typical number of implants is three, but depending on the size of the patient and the patient's anatomy, our clinical advisor for this report suggested you could use as few as two, or you might need to use as many as four. Some systems use decortication combined with the implants for immediate fixation and then insert a bone graft to achieve a fusion. An example of that device is the Simmetry system, which is shown down here at the bottom. So, in principle, they do similar things, but they have, there are differences among the different systems, in terms of the shape of the implant or screw and whether or not bone graft is used separate from the implant itself.

So, 15 devices with FDA 510k clearance are currently on the market in the U.S., and as you have heard, 510k clearance is based on evidence that a device is substantially equivalent to a device already approved by the FDA or that was marketed prior to 1976. So, we note that none of these devices were required to go through the more rigorous premarket approval process. There are also five devices with Title 21 CFR approval currently on the market. This is the approval that applied to devices that have allografts or biological materials. Then, there are a couple devices that are not currently on the market. One has 510k approval. The other one is in Europe. Then, just as a reminder, open procedures could be performed with cleared or approved SI joint fusion devices, but they also could be performed using orthopedic plates, screws, tools, instruments that are already cleared by the FDA, and which may not necessarily be specifically designed for SI joint fusion.

Okay. So, as you heard, this topic was selected for review by the State because of high concerns for safety, efficacy, and cost. So, next, I'll just briefly go through our methods. This is the [inaudible] analysts [inaudible] guiding the review, which again, focuses on the populations with chronic SI joint pain that evaluated SI joint fusion interventions. There were three main research questions, one related to effectiveness, one related to safety, and one related to cost. We set aside several sub-key questions, specifically for comparative effectiveness and harms of alternative surgical procedures.

This slide summarizes the study selection criteria. So, we focused on adult populations with chronic SI joint pain that used standard diagnostic criteria

and evaluated open or minimally-invasive surgery against a comparator of either active non-surgical treatment, placebo, or no treatment. We had satisfied several efficacy outcomes, including pain, functioning, patient satisfaction, quality of life, opioid use, and return to work. For comparative effectiveness of alternative procedures, we also satisfied some intermediate outcomes, such as length of stay, non-union. For safety outcomes, we selected studies that reported adverse events, including surgical morbidity or the need for revision surgery. And then for cost outcomes, we selected studies that reported cost or cost-effectiveness and quality or disability adjusted life years. For the studies selected for efficacy or cost, we did require a comparator. For the safety question, we allowed uncontrolled studies.

Then, finally, we only selected studies from countries that were conducted in countries categorized as very high on the U.N. Human Development Index. These are countries like the U.S., Canada, Australia, New Zealand, uh, the countries in Western Europe, Japan, South Korea, and a handful of Middle Eastern Countries.

We conducted risk of bias assessments on all included studies. We used different risk assessment tools depending on the study design, but all studies were assigned as having a high risk for bias, meaning there are some serious concerns, very serious concerns about the conduct or design of the study. Some concern is the middle category or low risk for bias. That's the lowest category. So, these ratings apply at the study level, unless we determine different outcomes within the study require different ratings. As a reminder, the domains we assess during risk of bias or randomized trials include the process the study uses for randomization and allocation concealment, performance bias, which includes things like blinding of participants and clinicians, and deviations from intended intervention, missing data and attrition, outcome measurement including the use of validated measures, and outcome assessor blinding, and selected outcome reporting. For observation studies, we also assess the risk of bias introduced by confounding. I want to note here, because I think it will come up as you deliberate on the evidence that risk of bias is really on a continuum. It's not really a binary concept, and current methods [inaudible] emphasize and evaluate not just whether any factors contributing to a risk of bias are present or absent, but really thinking about how that risk of bias, how that factor substantially influences the effect size or the direction of effect that's being observed.

And then lastly, we generated quality of evidence ratings using the grade approach. I know we have some new members here. So, I'll take some time to just remind everybody about the grade approach. So, grade is

applied to a body of evidence. So, that means one or more studies that contribute to its comparison and specific outcome, and it's determined by something by domain, and those domains are listed up here. So, risk of bias that we just discussed is one of those domains. The other domains include things like the consistency of findings across studies was in the body of evidence, the directness of the measure used, the precision of the estimates, which relates to the sample size and whether those studies were adequately powered, um, and then publication bias. The assessment of these domains leads to a rating of very low, low, moderate, or high quality. The next slide provides some language for interpreting the different quality levels, but I want to emphasize that the rating that we assign under grade, that represents the certainty that we have in that body of evidence, based on all of the domains. So, it's separate from the risk of bias. We might find some individual studies. As a reminder, bodies of evidence comprise of randomized trials start at a high rating by default, and then we downgrade them to moderate, low, or very low based on the domain assessments. Bodies of evidence of observational studies, they start at a low rating, and they get downgraded, again based on domain assessments, or they can also be upgraded based on several factors at the bottom here, but those are very uncommon, and we did not upgrade any studies in this body of evidence.

So, as I mentioned, here are the definitions for interpreting the different grade levels. I won't read them to you verbatim, but as you can see, they really reflect the continuum of very low certainty to very high certainty.

Then, finally, part of the last piece of our approach is to assess the quality of, or identify clinical practice guidelines using the appraisal for research and evaluation tool with this tool and overall score of between one, which refers to the lowest possible quality, and seven, which represents the highest possible quality defined.

Okay. Moving on to the main event, the results. So, first, we're going to go to the primary research statement, then we'll tackle the CPG stuff at length. So, here is a summary about search results. We identified 662 titles and abstracts, which then led to us screening 113 full text articles, and out of that, we identified a scope of 43 studies that were published in 50 different articles, and the breakdown of studies by key question is shown in the boxes. Then, we also identified two publically available clinical practice guidelines. That may become important when we talk in the discussion.

So, to orient you a bit to the results, let me just describe the three comparisons that I'll be presenting. So, first, I'll be presenting the study

that evaluated SI joint fusion, minimally-invasive or open, to conservative management or neurosurgery. The ink slide would be colored in blue, and they address all three research questions. Next, I'll be presenting studies that evaluated minimally-invasive sacroiliac joint fusion to open fusion, and these slides will be colored green, and they address only the efficacy and safety questions. Then finally, I'll be presenting the one study that compared two alternative minimally-invasive procedures, and these slides will be gold or yellowish, and they only address the safety question. Then, lastly, I'll talk about the uncontrolled studies.

Okay. So, first the, the first comparison is minimally-invasive SI joint fusion compared to conservative management, and we identified three studies for this comparison. All of them compare the iFuse implant system to conservative management. So, the Insite and iMIA studies were RCT's we've already heard a little bit about. They're in the first two rows of the table. So, Insite was conducted at 19 U.S. centers, iMIA was conducted at 9 European centers. Both were sponsored by the manufacturers of the device, and the surgical intervention was the same in both trials, but the comparator is different somewhat. So, in the iMIA trial, conservative management consisted of optimization, medical therapy, individualized physical therapy, focused time mobilization and stability, at least twice per week for up to eight weeks, and then patient education. Finally, cognitive behavioral therapy was allowed, but not available at all of the sites. So, typically steroid injections and nerve ablations were not eligible for conservative management in either trial. Insite, on the other hand, used a step-wise approach to conservative treatment that was directed by each site investigator that included physical therapy, which nearly all participants underwent, therapeutic joint injections, which about three-quarters of participants underwent, and radiofrequency ablation, which about 45% of participants underwent. Both trials allowed crossovers after six months of follow-up. So, we rated both of these studies as having some concern for bias for up to and including six months, primarily because of the lack of treatment blinding and the lack of outcome assessment planning. The study in the third row by Vanaclocha is a retrospective controlled covert study conducted in a single center in Spain that also evaluated iFuse; however, there were two comparator groups in that study. One was conservative management, which included smoking cessation, weight control, and physical therapy for at least three months, NSAIDs, and therapeutic joint injections. The other comparator group in that study was radiofrequency nerve ablation. We rated this study as high risk of bias, mainly because of the high degree of attrition and missing data that was reported, and also because we had concerns about confounding a selection bias related to the observational study defined.

Mika Sinanan: I'd like to ask you a question. We have talked about patients being treated with conservative therapy, failing, and then getting assessed for surgical therapy. In these trials, had the patients gone through an extensive... oh, okay. Thank you.

Leila Kahwati: Next slide. So, let me tell you a little bit about the enrolled participants in all three of those studies. So, the diagnostic criteria used in both RCT's and in the cohort study were similar. So, all studies required chronic symptoms. So, in the iMIA trial, at least six months of failed conservative treatment was required. In the Insite trial, the patients were characterized as failing conservative treatment, but there was no time requirement set by this part of what was reported in the study. In the cohort study, again, these were people who had conservative treatment for at least three months. All the studies required a positive Fortin Finger Test and at least three provocative examination findings, and then a 50% or greater reduction in pain after an SI joint block. The two trials also required a baseline visual analog pain score of higher than 50 mm, again, on a scale of 0 to 100, and an Oswestry Disability Index of treater than 30 points, and that scale is also 0 to 100. The baseline VAS score in Insite was 82 mm in both groups, so very high levels of pain, and in iMIA, it was 73 and 77 in the two groups. The mean duration of pain across the groups in the studies was between three and seven years, and as previously noted, about one-third of the study population in both the trials and the cohort study had a history of prior lumbar spinal fusion. I think there are several ways to think about this last characteristic, because we don't know from a study report the reason for the prior lumbar fusion or whether patients presenting for study entry had new onset low back pain since their lumbar fusion surgery, or just had persistent pain despite their lumbar fusion surgery. Some experts chalked it up to a prior lumbar fusion alters the biomechanics of the SI joint, resulting in a faster degenerative process, which then leads to pain. Others had suggested that focus was low back pain that we see people with prior treatment may not have had SI joint pain considered or ruled out as the initial source of pain. So, they continue to have pain despite the lumbar fusion, because perhaps they were misdiagnosed. I think the jury is out on this.

So, now we'll turn to the findings. So, because all the findings, I tried to organize them, and they're kind of [inaudible] a few minutes orienting you to the layout of the slide. Again, the comparison here is, um, minimally-invasive fusion with iFuse compared to conservative management. So, each outcome is presented in a box. So, for example, the one at the top is change in pain at six months. The measure used to define the outcome is listed here. So, this is a visual analog scale for pain measured from 0 to 100 mm. The minimally important difference on this measure is about 7

to 11 points. In the left side of the box is the body of evidence. So, there were two RCT's, Insite and iMIA trial. Below that is our assessment of the Vanaclocha, rated as moderate, and this is the direction that favors iFuse compared to conservative management. In the right side of the box, there is a narrative summary of the findings. So in this case, participants who were allocated to iFuse experienced a 40.5 mm greater improvement than participants allocated with conservative management in one study and 38.1 mm greater improvement in the other study. Findings were statistically significant in both studies. As I mentioned.

John Bramhall: Question? The millimeter, that's distance along an analog scale?

Leila Kahwati: Yes.

John Bramhall: Is that what that is?

Leila Kahwati: 0 to 100.

John Bramhall: Alright. Thank you.

Leila Kahwati: Yeah. So, these are the difference between groups. So, as I mentioned, Insite trial, they started at a baseline of 82, and they dropped to about 30. So, they had a 52-point reduction in the fusion group. The conservative management group only dropped to about 70. So, they only had about a 12-point reduction. So, this 40 represents the difference in difference, if you will. Any questions about the layout of the results? Otherwise, I'll go a little bit faster through the rest of them.

Janna Friedly: I'm confused. So, can you... that -40 confuses me. I understand what you said about 12 points and...

Leila Kahwati: Yeah. Yeah.

Janna Friedly: ...a 30-point difference, but...

Leila Kahwati: So, the surgery group reduced their score by 40.5 mm more than the conservative management group, which, because the way the scale is 0 to 100, 100 is worst pain, that's an improvement in pain. Okay. The bottom box [inaudible] for outcome of change in pain at six months to three and a half years. So, this body of evidence is also visual analog scale. This is the body of evidence from the cohort study. It's a longer timeframe of follow-up. So, it... people would follow-up at different intervals. So, that's why it's six months to three and a half years. We graded this evidence at very low quality favoring iFuse, and there were, again, significantly larger

improvements in pain in the iFuse group compared to conservative management. The between groups difference was... so this study annoyingly measures in centimeters. So, it's 0 to 10 cm. So, this study had a -6 cm, if you can think of, which is equivalent to a 60 mm difference. So, it's a larger treatment effect than what was observed in the trials. Then remember, I said there were two comparator groups. So, compared to denervation, the same group difference was 4.5 cm, or 45 mm.

Mika Sinanan: So, question, in the quality of evidence for the first one...

Leila Kahwati: Yes.

Mika Sinanan: ...in your previous slide on quality of evidence, a very serious concern would drop it two levels. A serious concern would drop it one level. So, because of the bias, that would have dropped it at least one level.

Leila Kahwati: Yeah. And that's why it was dropped.

Mika Sinanan: Okay. So, you're...

Leila Kahwati: Because of risk of bias.

Mika Sinanan: ...saying that absent the bias, it would have been four...

Leila Kahwati: Correct.

Mika Sinanan: ...a level four.

Leila Kahwati: Yeah. The results were precise. They were consistent. The measures were direct, and we found no evidence of publication bias. So, risk of bias is really the only domain that there were issues for.

Mika Sinanan: Thank you.

Leila Kahwati: Moving on to the next outcome, which is change in physical function at six months. We rated the quality of evidence as measured by the Oswestry Disability Index as moderate for favoring iFuse. Again, this is based on the two RCT's, and very low for favoring iFuse based on the one controlled cohort study. Again, the outcome measurement in the cohort study was over six months to three and a half years. The difference in improvement with iFuse compared to conservative management was similar between RCT's and the controlled cohort study. So, across all three studies, the difference between groups was about 20 to 25 points. So, the groups that received surgery had 20 to 25 point more reduction in this index, which

indicates improvement in function. Minimally important difference on this index was about 8 to 11 points.

Moving on to the next outcome, which is quality of life, we rated the quality of evidence as moderate for favoring iFuse for change in quality of life at six months based on the two RCT's. Two studies measured quality of life using the EuroQol-5D. Both observed statistically significant greater improvement in participants allocated to surgery compared to conservative management. This particular measure ranges from actually less than 0. So, I think it's -0.59, because there apparently are states of health that are worse than death, to 1, which is perfect health. The MID and the EuroQol-5D is about 0.07. So, the effect size seen in the change or difference is about three times the minimally important difference. Similarly, one study also reported using SF-36 and there are statistically significant between those differences on both the physical component, summary score, and the mental health component summary score. The magnitude... the mainly important difference on these measures is about three.

Moving onto opioid use at six months, so we rated the quality of evidence as low for no difference between SI joint fusion and conservative management based on the one RCT that reported this. Although the absolute incidence of opioid use was 12% lower, among participants allocated to iFuse, this difference was not statistically significant. I think Dr. Transue showed you the actual percent of participants that were... or the change in opioid use between the groups, but it was not statistically significant.

In contrast, we rated the quality of evidence for opioid use at six months to three and a half years as very low for favoring iFuse based on the controlled cohort study. So, in this study, there was a significant difference in the number of oral morphine equivalents between participants who have received fusion compared with those who received either radiofrequency ablation or that had conservative management, and you can see the difference in the oral morphine equivalents they were using at the time of follow-up, and those were all statistically significant differences. So, this is probably the only outcome where there is a difference between the RCT evidence and the observational evidence.

John Bramhall: So, this is still a very low rating.

Leila Kahwati: Yeah.

John Bramhall: In your introduction, you commented that some studies, the randomized control could be upgraded. This is a pretty... this is a ten-fold difference in morphine equivalents. Is that the kind of difference that typically would lead to an upgrade?

Leila Kahwati: Um, perhaps, but only probably in the setting of no concern for bias, which we did not have. This study has concerns...

John Bramhall: Right.

Leila Kahwati: ...for bias and that would probably have still made us want to keep it, not upgrade it.

John Bramhall: So, you make a judgment, these numbers are actually generated with some concern for bias.

Leila Kahwati: Exactly.

John Bramhall: Alright.

Leila Kahwati: It's rather uncommon... I can't recall too many instances where we've actually upgraded evidence from observational studies. I think... I mean, can you think of incidents where we've done that? Yeah. I mean if we had multiple studies in the observational study, and they all showed this difference, that might make us want to upgrade it. Okay. Moving on to safety outcomes, so we had set the quality of evidence as low for no difference between SI joint fusion and conservative management for serious adverse events based on the two RCT's, and these are all cause serious events meaning they're events that happened during the study period. So, they're not just events that are either definitely or probably related to the device, and you can see that the frequency of events between groups is similar. So, in one study there were 21 events in 102 participants, that's about 21%, and then there were six events among 46 conservative management participants. That's about 13%. So, slightly higher in the surgery group, but the difference was not specifically significant. In the evidence study, there were eight events.

Gregory Brown: So, I'm sorry. What's a serious event in a conservative study?

Leila Kahwati: So, that... just like the FDA for a definition... so they're events that usually declare medical attention... they don't necessarily require hospitalization, but they are, like, a threat to life, limb. They require addressing.

Gregory Brown: Okay. So, can you...

Leila Kahwati: So, if something like [inaudible] of the flu is going to get counted as a serious adverse events, because it was a hospitalization.

Gregory Brown: Right. So, you're including all... so you have no source of adjudication, as to whether these serious events are related to the treatment?

Leila Kahwati: Yeah, so good practice, what the standard of practice is, studies are supposed to report all serious adverse events regardless of... because if you let them decide what's serious and what's not, or what's related and what's not, that's when a lot of bias creeps in. So, the best tactic is, you report all cause serious events. Then, a lot of studies will then report, okay. These are the ones we definitely think are related to the device or the drug or whatever it is you're studying. These are the ones that, like, would probably be related, but the best practice is to report all cause, because that's the least bias estimate.

Gregory Brown: So, I guess what I'm trying to understand is, is what sort of conservative treatment can cause a serious event?

Leila Kahwati: Well, yeah, do you want to comment on that?

Coner Kleweno: I was just gonna make an analogy. If you were, you know, 30 years ago comparing open reduction internal fixation of the tibia fracture to a cast, and in your conservative group, the casting group, you saw a higher rate of pulmonary embolism, you say well, how can a cast cause pulmonary embolism. At that time, you'd be, like, surprised, but it may not be a causal but association of limiting treatment may lead to an effect of negative consequences. In general, if you're withholding a potentially beneficial treatment, could that lead to a higher rate of untoward consequences, theoretically?

Leila Kahwati: Yeah. And the other reason for recording all cause events is because of randomization. The same number of probably not related events should occur in both groups so that if you see a difference in all cause events, they ought to be related to a device, or a procedure, or whatever it is you're doing, because the number of unrelated events should be distributed equally between groups if you're randomization was done properly.

Janna Friedly: I'd just like to add, I mean, they did publish what they considered to be procedure and surgery-related adverse events in at least the Insite in the trial setting.

Leila Kahwati: I think we have the name of the evidence tables in the report. Cindy will look while we're going here.

Gregory Brown: Thank you.

Leila Kahwati: Okay. So, in the control cohort study, there were no serious adverse events reported in either group. So, we assessed the evidence as very low for no difference.

For the incidence of revision surgery, we assessed the evidence as moderate quality based on the RCT's and is very low quality based on the control cohort study. So, we don't do a comparative assessment here, because obviously the people in conservative management, revision surgery doesn't make any sense for them. So, we're really... our strength of evidence... our quality of evidence rating is really assessing our confidence in the estimate of the incidence estimate. So, in the incidence of revision surgery among participants in one study was 3.4% at two years, and that was among the 89, I believe this first one is Insite, 89 iFuse participants who had follow-up data available at two years. The incidence in the other study was... and then in that same study, the 30 conservative management participants then crossed over to surgery. The incidence of revision surgery was 2.6% in that group. So, those were reported separately. So, that was with Insite. Then, in the other study, there were no revisions among the initial 52 participants allocated to iFuse, and there was one revision amongst the 21 crossover patients.

Mika Sinanan: You alluded earlier to the possibility that the fact that 30% had lumbar fusion might indicate they were inaccurately diagnosed initially as having a lumbar source of pain and then, because they didn't have a response, were getting treatment for SI. Right? Or it could be the other way, too. It could be treated for SI, but have a lumbar source of pain.

Leila Kahwati: Yes.

Mika Sinanan: In that case, is revision surgery, does that include lumbar surgery?

Leila Kahwati: No. This is SI joint fusion surgery.

Mika Sinanan: So, it's only... or going back for a second operation on the sacroiliac joint.

Leila Kahwati: Yes. Correct. What we don't know, again, with this... we talked to our clinical advisor about the revision surgery, whether more revision surgeries would be performed open versus using a repeat minimally-invasive approach, or our advisor seemed to think that probably typically most

would do another minimally-invasive approach, unless there was some reason that that was not feasible or ethical, depending on the reason for the revision.

In the control cohort study, there were no revisions surgeries reported amongst the participants who received iFuse.

Before we move on to the next comparison, I wanted to provide you with a summary of the efficacy outcomes recorded beyond six months. As you heard, crossovers from conservative management to surgery were allowed after six months in both trials, and as you might expect, the participants who crossed over had higher mean VAS pain scores and higher Oswestry Disability Index at the six-month follow-up period, indicating worse pain and functioning compared to those who did not cross over. Among those allocated to fusion, the changes in the low back pain scores that were observed at six months largely persisted at one year. In the iMIA trial, 69% of those allocated to fusion had at least a 20 mm improvement in pain compared to 27% of those allocated to conservative management who did not cross over. In the Insite trial, 81.6 of those allocated to fusion had at least a 20 mm improvement compared to 12.5% allocated to conservative management. For this particular analysis, participants of crossover surgery were considered as failures. So, this was the way that the investigators elected to mitigate the bias introduced by allowing crossovers. A similar pattern was observed for physical function measured by the Oswestry Disability Index, and now the improvement seen at six months in function persisted at periods after six months and were significantly larger than improvements in the conservative management group.

Mika Sinanan: Question about the VAS. When you present that, do you say, by the way, this is where you were last time? Or do you give it to them blank.

Leila Kahwati: No. You give it to them...

Mika Sinanan: You never say anything about what they previous... okay.

Leila Kahwati: Okay. Okay. I mean...

Mika Sinanan: That's the way...

Leila Kahwati: ...that's the way it should be, and that's another important point, because in trials, or in prospective trials, there is some control over how you measure these outcomes, you have research assistants or trained researchers who administering the instruments in a standardized way. In a controlled cohort study, a lot of these studies are largely relying on

existing clinical data, the medical record, or data collected through the course of clinical practice, and there's generally less standardization of how the outcomes are measured, which is why you'll see in most of the studies we evaluate from that observational evidence have at least some if not high concerns for bias.

Okay. Next, we'll look at the very small body of evidence related to open fusion compared to no surgery. This is the only study to be identified. It was a retrospective control cohort study from a single center in Norway that compared open fusion using a dorsal approach to no surgery. No specific device was named as being used for the open fusion, and no details about what percent from the no surgery group received were provided. So, we really have no information about the comparison group. This study scanned a time period from 1977 to 1998. So, it was a very large, several decades, and the method of diagnosis was physical examination and imaging. We rated the risk of bias in a study as high, because of confounding selection bias in the way in which outcomes were measured. They only recorded three efficacy outcome eligible for recording here. All were at 11 to 23 years follow-up. So, pain, physical function, and quality of life. No significant between group differences were observed in any of these measures. No safety outcomes were reported by this study. We ended up rating the quality of evidence as very low for all these for no difference between groups. And that's probably all that's worth saying about that study.

Moving on to the next comparison, minimally-invasive surgery compared to open fusion, we identified three studies. All were controlled cohort studies comparing iFuse to an open approach. Two of the studies in the first two rows used an open anterior ilioinguinal approach, and the last study used an open posterior approach. These are all U.S. studies conducted in the U.S. The first study there was a single U.S. center. The second study was conducted by the same author at two U.S. centers; however, they needed the same comparator patients, 22 patients were the same in both studies. The study in the third row was at seven U.S. centers, and that was conducted between 1994 and 2012.

For change in pain, we assessed we had very low quality for favoring iFuse based on one control cohort study. Only one of these three studies reported pain. Participants who received iFuse had a 3 cm or 30 mm greater improvement on pain, as measured by the VAS, and this was in the repeated measures analysis over two years. For change in physical function, we assess the evidence as very low and we noted mixed findings. So, in one study, participants who received iFuse had a significant... statistically significant improvement in the Oswestry 33 point difference,

so quite large compared to participants who received open fusion. In the other study, however, the between group difference was only 4.9 points and as you'll note, that's less than a minimally importance difference, and that difference was not statistically significant. So, we could really not conclude a direction of effect from that body of evidence.

With respect to hospital length of stay, we assess the evidence as very low quality favoring iFuse based on three control cohort studies. Participants who received iFuse had significantly shorter length of stay. The range of difference in length of stay was between 1.3 and 3.8 days across those studies.

For adverse events, we assess the evidence as very low quality for no difference between iFuse and open fusion with respect to adverse events based on the three cohort studies. So, no intraoperative complications were reported in any of the three studies. The frequency of postoperative complications were similar between groups. So, the range, though, of the events was quite wide. So, it was anywhere from 2.3 to 35% across all of the groups minimally-invasive and open. We'll come back to that issue in a little bit. We also assess the evidence as very low quality for mixed findings with respect to revision surgery. So, again, this is based on three control cohort studies. So, two of the studies recorded infrequent revision in both groups. So, there was one to two revisions in each group for, I believe, the two Ledonio studies. Then, in the third study, there was significantly fewer revisions with iFuse, and it's quite a big difference. So, the absolute risk difference was 51.3%. The relative risk was 0.1. So, that's a fairly large effect, and it was significantly statistically significant. So, we, again, couldn't... because of the inconsistent findings here, we really couldn't conclude a direction of affect.

Then, finally, the last comparison was minimally-invasive SI joint fusion with iFuse implants compared to percutaneous screw fixation. There was one study for this comparison, which was a control cohort study conducted at a single U.S. center. This study only recorded one outcome for eligible for inclusion, and it was the incidence of revision surgery. We assessed the evidence as very low quality favoring iFuse. There were significantly fewer revision with iFuse compared to percutaneous screw fixation. There were 4.6 revisions in iFuse compared to 65.5% in the percutaneous screw fixation.

So, next I'm going to briefly summarize the safety outcomes that were reported from 32 uncontrolled studies that we identified. So, as I had already mentioned, a lot of these observational studies were... these are all observational studies. They're uncontrolled. Many were conducted

retrospectively using data from medical records. There were a few that were conducted prospectively in uncontrolled trials, and I will point those out where relevant. So, this is a summary table describing the procedures that were used in the 32 uncontrolled studies. In the first row, these are the eight studies that evaluated fusion, and you can see they largely used different approaches, different techniques. In the next row, you can see that of the minimally-invasive, or other techniques, the most commonly evaluated one was iFuse. There were 13 studies total that reported on its use. Then, most of the other devices were only reported in between one and three studies. So, I'm not gonna say too much about those. The data is in the evidence report, but I do want to mention the last study here in the table. So, this was the study that used claim database on the CPT codes, 27279, the code for minimally-invasive SI joint fusion. I'll give you the results in a minute, but it's not compared to what devices were used. So, it's just based on CPT codes. So, we don't know if it's iFuse. We don't know... it's probably a mix of different devices.

So, I guess the biggest takeaway from this body of evidence is that the studies use very different ascertainment methods for safety recording, and it's a major limitation of this body of evidence, because, again, they are retrospective. We don't know how thorough or rigorous they are looking for adverse events. We don't know... there's a lot of inconsistency in the grouping and the definitions of adverse events. So, that's the major limitation of this body of evidence. Two key findings, though, to highlight. So, this is the last study in the table on the previous slide. So, this is using insurance claims. It was from 469 beneficiaries who underwent fusion based on the CPT code, and this was from 2007 to 2014. The incidence of complications, again based on claims, was 13.2% at 90 days and 16.4% at six months. The most common complication recorded was neuritis or radiculitis.

Among the 13 studies using iFuse, the incidence of device or procedure-related adverse events, again not all cause adverse events like what was reported in the trials, but this is device or procedure related events, ranged from 0% in some studies to up to 30% in other studies. Much of this variability, again, likely had to do with differences in how studies ascertained adverse events and their reporting. The incidence of revision surgery across these studies also were variable. It ranged from 0% in some studies to 8%. I will highlight findings from one study, in particular. So, this study used a post-market surveillance database from the manufacturer that had 11,388 participants in it that had received iFuse. Using this data, the authors calculated a revision incidence of 2.8% over a median follow-up of about four years, and 63% of those revisions occurred within the first year.

Gregory Brown: So, for database reporting, that is purely if the surgeon chooses to report?

Leila Kahwati: So, this specific database is maintained by the manufacturer. So, I think if the revision surgery involved a second device, a second iFuse device, then it would show up in the database. So, what I don't know is whether patients received a revision surgery with a different device, would be incorporated here.

Gregory Brown: Oh, they don't know what they don't know?

Leila Kahwati: Yes.

Gregory Brown: Yes.

Leila Kahwati: That's very philosophical.

Gregory Brown: Yes.

Leila Kahwati: Okay. Moving on to the cost question. We identified three studies providing outcomes related to cost or cost-effectiveness. All were reported using U.S. dollars and U.S. input. Two studies were conducted by the same author, the Ackerman... two Ackerman studies. So, the one in the first row here focused on a commercially insured population with a mean age of 45.2 years old, and they have looked at a comparison of cost between minimally-invasive fusion and non-operative care over a three to five year time horizon. So, this is a cost modeling study. The authors used inputs based on studies using the iFuse implant system. The second study in the second row used the same comparison, same methodology, but they focused on the Medicare population. So, they used a starting age of 70 and modeled lifetime costs based on life expectancy of about 84 years. So, it's lifetime cost, but you can think of it as a 14-year timeframe that they looked at. The study in the third row is a cost-effectiveness analysis comparing iFuse to non-operative care. It used a follow-up time of five years and used EQ-5D as the utility measure for discriminating quality of adjusted life years.

So, we evaluated the evidence as very low quality for both cost over three to five years in the commercial population. So, that's the top box. Then, very low for lifetime costs in the Medicare population. It's hard for cost-modeling studies to get anything above a very low or low, because they're not trials, just for some perspective. I believe the reason we downgraded these from low to very low was imprecision, because they didn't provide estimates around... confidence intervals around the values. So, in the

commercial population, minimally-invasive fusion costs $14,000, a little over $14,000 more over three years and a little over $6000 more over five years compared to non-operative care. In contrast, lifetime costs, which again, these were the costs over about 14 years in a Medicare population, were just over $3000 less with iFuse compared to non-operative care.

Tony Yen: I just have a question, if you parsed it out provider fees versus facility fees for those... if you were able to get that detail?

Leila Kahwati: We'd have to look what they used for their [inaudible]. Do you remember Cindy? All direct costs. So, I assume that would be both. Yeah, because these are from a payer perspective. So, they are not gonna include indirect costs, like, time off from work and time... parking for their visit. So, it's direct medical costs.

Tony Yen: But it's a summation of both the fee to the provider and the facility?

Leila Kahwati: It should be. We can double check, but if it's direct cost, it should be. Yeah. These were 2012 dollars. There was one cost-effectiveness study that we evaluated as very low quality. This study, authors estimated the cost per QALY adjusted life year gain for iFuse compared to non-operative care was a little over $13,000 over five years. The breakeven costs, in other words, that's the point at which the cost per additional QALY becomes 0 dollars, that breakeven was at 13 years.

Moving on to clinical practice guidelines, so we identified two publically-available clinical practice guidelines, and I want to point out that there is coverage criteria that are out there. There is clinical practice guidelines. There is some overlap between what you would consider a clinical practice guideline versus what you would consider a policy related to coverage. So, we tried to focus on things that were guidelines and less designed to focus on informing what coverage criteria should be. So, the first one is from the National Institute for Health and Care Excellence in the U.K. This is not one of their large comprehensive NICE guidelines. This is a format of something they called intervention procedure guidance document. They have hundreds of these for different procedures. We assess the quality of this guideline as a four on a scale of one to seven where seven is the highest possible quality. This guidance document concluded that the current evidence is adequate to support the procedure, but they did have some caveats in the guideline about it being done by properly trained surgeons who do image-guided surgery with experience in the procedure.

The second one is AIM Specialty Health. AIM is a [inaudible] of Anthem, and they focus on developing clinical guidelines. We assessed the quality

of this guideline as a three out of seven. This guideline concludes that minimally-invasive fusion with iFuse may be considered medically necessary when clinical criteria are met. I think that Dr. Transue already showed you some of the criteria, or all of the criteria that they have in their guidelines. I would note that there are other clinical criteria or coverage that exists, but they are often proprietary or behind [inaudible]. So, you might have to be at the hospital or a payer and subscribe to one of these services, but then you can get somebody else's curated coverage criteria.

So, those are the findings. Next, I'm going to briefly recount them with an evidence map and then discuss some of the implications and limitations. So, this is the evidence map summarizing iFuse compared to conservative management. So, the outcomes are located along the Y-axis here. Each space on the map indicates the body of evidence for the outcome. We have detected the bodies of evidence from the randomized trials separately from the bodies of evidence from observational studies. So, a rectangle space is a short to medium term outcome, generally up to six months, followed by oval indicates longer term outcomes, generally beyond a year. The color of the shape represents the quality of evidence, according to grade. So, that is very low. Orange is low. Yellow is moderate. Finally, the location of the shape, along the X-axis indicates the direction of affect. So, anything over here on the right is an outcome where iFuse is favored. Anything here in the middle is where there is no difference between iFuse and conservative management. So, at a glance, you can see that most of the efficacy outcomes, except for opioid use, iFuse was favored. There was no difference for opioid use and in serious adverse events.

This next comparison is for open fusion compared to conservative management. Again, there is only one study in this evidence base, and it had no difference in pain, function disability, or quality of life. This particular study, if you recall, is follow-up over 11 to 23 years, so very long follow-up.

Then, finally, this summarizes the evidence comparing iFuse to open fusion. As you can see, all the outcomes evaluated were very low quality, according to grade, while findings for the effect on pain and length of hospital stay favor iFuse, the finding on physical function were mixed for these two studies, as well as for revision surgery. So, no difference in serious adverse events, some mixed findings for physical function and revision surgery, and benefit for iFuse for pain and length of hospital stay.

Limitations of the evidence base, so although we focused mostly on the control studies in this report, you'll note from our [inaudible] identified

are, in fact, uncontrolled, and we only reported safety outcomes from these uncontrolled studies. But as I mentioned earlier, there are many limitations in these uncontrolled studies. A lot of them were small sample sizes. A lot of heterogeneity in how they ascertained and reported adverse events and revision surgery. Secondly, this is a body of evidence, or at least the comparative evidence, that essentially focused on iFuse. That's the only device for minimally invasive fusion, for which we have comparative evidence for you to consider. Third, the outcomes reported in the studies of open fusion are quite limited, and based on clinical practice patterns is a scan of ongoing studies in the [inaudible], I think it's unlikely that future research is probably going to be conducted on open fusion for this condition. So, the relevance of these outcomes are uncertain. Then, finally, some risk of bias limitations, because RCT evidence base, as you heard, were not blinded. Although it's very challenging and often not feasible to blind surgical procedures, the lack of blinding still, nonetheless, imparts a risk of bias, particularly around outcome measures that are reported by patients themselves, so, things like pain and physical function. So, we don't necessarily excuse these studies, because it's hard to blind them. Right? But we do... we don't necessarily consider a lack of blinding a complete fatal flaw that makes the study worthless for interpretation. The important question, really, is could the lack of blinding be responsible for the entire treatment effect observed. In our opinion, it would be difficult, I think, to attribute a 40 mm difference in the VAS entirely to the lack of blinding. Even if the true effects were only half of that because of the lack of blinding, that's still a 20 mm difference, which is above a clinically minimally important threshold. The controlled observational study [inaudible] issues related to confounding, which were really not well managed through design analysis, and had a lot of issues with respect to selection bias. For example, many of the studies require patients, because they are retrospective, to have a full year of follow-up to be eligible for the study. What that basically means is, anyone who died or had a serious complication or moved away is not [inaudible]. So, that's a pretty major selection bias in those studies that are designed like that. Then, although some studies reported findings by subgroups, none really appeared to conduct a prespecified analyses. To address an earlier question that came up about effects in both groups, both the trials did do some subgroup analyses. Neither of them found any differences, and the group of patients with prior lumbar fusion compared to those who didn't get it. So, the treatment effects were similar. Then, one of those studies did subgroup analysis in the patients who had postpartum related SI joint pain, and there, again, were no differences in the treatment in that subgroup, but those are really the... a couple of the studies looked... they also looked at smoking and a few other more demographics of those groups and found no differences.

So, you've already seen a little bit of the existing payer coverage, and this is, as I think we've previously mentioned, is a little bit in flux. So, this is what we captured as of October 1st, but there have been a few updates, since then, and I'll just quickly mention them verbally. So, CMS does not have a national coverage determination, but all of the Medicare administrative contractors actually do cover this procedure, generally with criteria, including the one that operates in the state of Washington, that's Noridian. Two payers cover minimally-invasive fusion for chronic SI joint pain when certainly clinical criteria are met, and that's Regence. Then Tricare covers procedures associated with the 27279 CPT code. So, most of the other Washington State commercial insurance do not cover the procedure, but Blue Cross/Blue Shield association payers from other states, many of them do when clinical criteria are met, and as of January 1st, the Premera federal employee program is including this on a list of procedures that will be covered, although it will require prior approval. Based on information supplied to us by the manufacturer, 44 state Medicaid programs cover iFuse, as of May 2018. I do want to say that this is coverage specifically for chronic SI joint pain. Most of the payers do cover SI joint fusion in the cases we discussed earlier of trauma injury, adjuncts to infection, sacral tumor, those kinds of things. So, this is coverage really here we're talking about for chronic SI joint pain.

Real briefly, there's three ongoing studies of SI joint fusion. All are minimally-invasive procedures. The first one is an uncontrolled trial of SI joint fixation system. The second is an extended follow-up from the two ongoing multicenter trials of iFuse. The third is a prospective non-randomized postmarket study of the Simmetry device. So, there are some future studies here, but we didn't identify a whole lot of ongoing studies, at least that are registered in clinical trials, I guess.

This next slide, basically, just summarizes the limitations of this Health Technology Assessment. So, we limited the scope to English language published data. We excluded efficacy outcomes from uncontrolled trials. We limited our search to three databases. We did not grade the body of evidence from uncontrolled studies, and as I mentioned earlier, some documents that you might consider seeking, but they are not publically available so are not necessarily represented here.

In conclusion, this is, I believe, the last slide, or no, second to last. This just kind of sums up the findings. So, among patients meeting diagnostic criteria for SI joint pain who have not responded to conservative management, minimally-invasive fusion with iFuse reduces pain more, improves function more, improves quality of life more, has uncertain

effects on opioid use, results in no serious difference in serious adverse events, and may be cost effective when compared to conservative management. In contrast, open fusion results in no longterm differences in pain, function, or quality of life when compared to conservative management.

Then, the last comparison, SI joint fusion with iFuse reduces pain more, results in a shorter length of stay but has similar incidence of adverse events, but an uncertain impact on function and revision surgery. Then, minimally-invasive fusion with iFuse results in reduced incidence of revision surgery when compared to percutaneous screw fixation. So, these last two slides are just at a high level summary. Questions that have not already been answered?

Gregory Brown: Actually, we were scheduled for a break from 10:05 to 10:15. I have 10:15. So, how about we take a ten-minute break and then do our questions?

Group: Mm-hmm.

Gregory Brown: Okay. We will rejoin at 10:25, ten minutes. Yeah.

Okay. I think we are a little past our time, but let's open it up to questions. Or did you have a comment?

Leila Kahwati: I can address two of the questions, and then you can... so, there was a question asked about the adverse events. So, in the iMIA study, these eight events in the iFuse participants, none were related to the device. Okay?

Gregory Brown: Okay.

Leila Kahwati: Two were related to the procedure, postoperative hematoma and postoperative neural impingement related to incorrect placement. Okay?

Gregory Brown: Okay.

Leila Kahwati: And the Insite trial, there were 21 events amongst iFuse participants, and two were definitely related to the device, and one was probably related. These were staple nerve root impingement, hairline fracture of the ilium, and contralateral SI joint pain.

Gregory Brown: And that's of the conservative treatment... did they feel that...

Leila Kahwati: Well, they don't adjudicate whether they're related to the device or not, because they're...

Gregory Brown: Okay. Obviously, there's no...

Leila Kahwati: There's no device.

Gregory Brown: ...device.

Leila Kahwati: Yeah.

Gregory Brown: Right? Okay.

Leila Kahwati: Yeah, but typically, in studies like this when you have a group that didn't really receive the device, the serious adverse events are things that caused hospitalization in the general population. So, MI, flu, pneumonia, falls, fracture, things like that.

Gregory Brown: Well, no. I... there is a nice study, I think it's out of Great Britain, looking at hip and knee arthritis, and patients with hip and knee arthritis with a disability for mobility have a 50% higher all cause mortality rate, probably related to cardiovascular due to lack of aerobic fitness and other issues. So, again, you could, in a... if you were looking at total means compared to... and actually it did fall... the number needed to treat for every eight hip or knee replacements you do, you save one cardiac event, probably one of the lowest numbers needed to treat you'll ever see in healthcare. Anyway, so you certainly have those kind of events, but I was just curious in this participation for a chronic pain problem what they might be, but, alright. Thank you.

Leila Kahwati: And then, the other question was about the cost. So, those were direct medical costs. So, it includes physician fees, facility fees, anything related to said procedure.

John Bramhall: Maybe it's a question more for Dr. Kleweno, but that study with the screws where there's a 63% revision rate, is that... do we think that's because you can revise the screws? It seems like the iFuse is a bit of a thrash to deal with, especially after time. You've got to use chisels to get these things out. So, is that what's going on? You can revise the screws and therefore you do?

Coner Kleweno: Yeah. So, that's a really good point that I wanted to comment on is that I think the revision rates published should be very carefully interpreted, and that is for exactly that reason, that the revision of the device mentioned

here, and data is only for iFuse is an exceptionally difficult one. It would be quite difficult. It has a high risk of morbidity, and thus, there is much less palatable for the treating provider. Not to cite too much anecdote is that I've seen a few patients that were referred to my practice with the device in who had... it's a little bit pejorative to say they had been abandoned, but they were not offered revision by the person that had put them in, and they were not offered any further treatment. So, I think that that revision rate is quite under... or maybe should be just considered with care in that because it's not easy to revise, your revision rates will be lower; whereas with a screw, again, the screws are in general use for treatment of trauma or stability, but you just put a screwdriver in and unscrew it. So, it's a 20-minute procedure to take a screw out. Now, what you do after that may be more difficult if you revise it to an open procedure, but I think that a take-home point is the revision rates published should be considered with caution.

Gregory Brown: I was just gonna make one more follow-up on that. The other thing is the timeframe. I think it had 74 to 92 or something. So, looking at screw plate fixation devices then versus now, they did not have locking screws. So, fixation in the sacrum can be very difficult, and other issues. So, it's not surprising that comparing 20 to 40-year-old technology to current technology, you're going to have a very different revision rate and issues. So, again, I agree with Dr. Kleweno on that.

Coner Kleweno: The other time is the time effect. How long something has been in practice or use could defect the revision rate, of course.

Sheila Rege: Question in terms of utilization with iFuse. We talked about the fact that with the point tenderness, it's usually unilateral. Does anybody have an idea that if it doesn't work in clinical practice, does the physician then try and do it on the opposite side? Is that fairly common that you do one side and then you kind of... if the pain is still there, you do the opposite side? Or what's the prevalence of patients getting it done twice or multiple times?

Coner Kleweno: The procedure?

Sheila Rege: The procedure.

Coner Kleweno: I don't have prevalence numbers. In general, when this procedure is made easier, i.e. an open procedure converting to an option for a minimally invasive, the incidence will go up, as we have seen with this, but I don't have prevalence or incidence numbers for conversion from one side to the other, because that leading question could be, if lumbar disease causes

adjacent segment SI joint disease, does stabilizing the left side then create more symptoms on the right side. So, I don't have that data though?

Leila Kahwati: I can tell you in the two trials, in the iMIA trial, seven of the 52 participants received bilateral procedure, and in Insite, 26 of the 102 received bilateral procedures.

Mika Sinanan: Were those done sequentially or done at the same time?

Leila Kahwati: I believe sequentially, but we can check on that. Cindy, would you check on that?

Mika Sinanan: And the portion of patients who were treated with conservative measures, conservative management who... so, the big population, conservative management not, because it worked, not offered any kind of fusion or further treatment? Do we know what that is? Presumably, this is a minority, a very small proportion of all patients with pain who are offered conservative treatment actually failed that and go on to treat with surgical treatment, or do you know?

Coner Kleweno: So, the only thing I can comment on is the data of the crossover of the trials was exceptionally high, and now again, that's a biased run trial. So, there's a bias towards conversion, I would say, in that.

Mika Sinanan: But those patients had already failed conservative treatment to even get into the trial.

Coner Kleweno: Right.

Mika Sinanan: So, it's conservative treatment failure into the trial, more conservative treatment failure again. So, it's not the same group as the initially conservatively treated group. Right? So, there are two different groups. It's a subset of the overall group.

Coner Kleweno: You're assuming that if you start at time zero, that some people will get better where...

Gregory Brown: But a part of... so if you started with 100 people that came in, first time with left thigh pain...

Coner Kleweno: ...right.

Gregory Brown: ...and you treated conservative versus immediate surgery...

Coner Kleweno: ...right.

Gregory Brown: ...you would get a very different outcome is what you're saying.

Coner Kleweno: Right.

Gregory Brown: Because you were already preselected by the fact they had to fail conservative treatment for six months, I believe.

Leila Kahwati: Six months within one trial. The other trial didn't put a specific timeframe ne. The study that probably gets the closest to what you're describing is the Vanaclocha controlled cohort studies. So, this is an observational study. Everybody was getting conservative treatment and failing. Then, some people were offered surgery, and the others just continued on in either one of two comparative... continued conservative treatment or radiofrequency denervation, but again, it's observational. So, how they decided who was offered surgery and who wasn't is not really clear.

Gregory Brown: There's no, we saw 5000 people and we put 500 in this trial or we saw...

Leila Kahwati: Yeah. Yeah. No.

Gregory Brown: ...600 people and 500 of them ended up in the trial.

Leila Kahwati: No.

John Bramhall: But Coner, you're sounding like you weren't that impressed with that crossover. I thought that crossover frequency was pretty high, and the way I looked at it was, you've got a cohort of people, all of whom have 'failed' conservative therapy. They're not getting better. Half of them get an intervention, which seems to improve their quality of life, and the other half, a lot of them, decide that's what I need, as well. So, you're right, Mika, the preselected for those are going to fail therapy right from the very beginning, but then, as you go in the two cohorts sort of demonstrate an activity, and it seemed to me, Coner, that a lot of those that were on conservative therapy did then benefit from an intervention. Is that the way you interpreted it, or you sounded a little doubtful?

Coner Kleweno: I guess I just... I wasn't surprised with the crossover, since I assumed that the conservative group had already failed like you said. We've already selected out from people that had plateaued and failed. The thing that was mentioned earlier, the conservative treatment was nothing. It wasn't a prescribed treatment plan that was controlled, that I understood. So, if they've already failed, they're going to continue to fail it and thus, it would

not be surprising that there would be a high crossover rate. Now, the effect of them getting better was of interest.

Seth Schwartz: I have two questions. First, when compared to the entrance criteria for these studies, it was... they had a better than 50% improvement on injection. Were those image-guided injections in both of those trials?

Leila Kahwati: Yeah.

Seth Schwartz: Okay. And then, the second question is, in this cohort study here, the radiofrequency denervation, we've heard nothing else about that, and I was just wondering if there's any information about that being a good comparator, or is that... do we know anything about that as a comparator?

Gregory Brown: [inaudible] for this afternoon.

Mika Sinanan: I would comment... it's not so much a question, but, uh, the use of color coding. That was great. It made it very clear both where the quality of the evidence is, and where the different questions were. I think it's a great model that we should be thinking about for future presentations.

John Bramhall: I agree. I thought this was a particular succinct presentation of the evidence. I appreciated it. Thank you.

Leila Kahwati: You're welcome. I apologize if anyone is color blind, 'cuz it doesn't work so well for you.

Sheila Rege: Can you comment... I know you've gone through the biases, um, in the Wang study were the authors employed by the manufacturer? All of them, right?

Leila Kahwati: No. Not all of them. I can't say for sure. I [inaudible], but the authors were not, I believe, employees [inaudible]. Could we double check?

Sheila Rege: And then Polly, I know two authors, the second and third author, were employees. Right? But I don't know about the Whang study.

Leila Kahwati: Well, Whang is the Insite study.

Janna Friedly: Both of those studies were funded by the same company, and they were, they were conducted at the exact same time over, you know, 2013, 2015, and one in the United States and one overseas with very similar protocols, and one of the people that is employed by the company and is acknowledged as one of the key people who designed the trial oversaw

the trial, conducted data analysis, and prepared the manuscripts was the same person in both trials. So, there were many investigators that the employees of the company were involved in the study. To what extent, I don't know, except that they were acknowledged as having a role in the design, the oversight, the data analysis, and the manuscript preparation. It's also the same author as the cost-effectiveness study, Share is the last name. So, one of the concerns that I have is, how independent were these two trials really, and should they really be considered two separate trials really... I mean, should they really be considered two separate trials for the purpose of, you know, a body of evidence about this device when they are essentially funded by the same company at the same time, just slightly different protocols based on location of where the patients were, Europe versus the United States.

Coner Kleweno: Sorry to repeat if this is well known, but some trials funded, as well as some consulting agreements with physicians require that research results and manuscripts are reviewed and edited prior to publication. And I don't know if there is any information you have on that. Obviously, the contracts are typically confidential, but that is... there is variation in what you can publish with the results of a study funded by industry. Some of them are basically required to be edited before publication.

Leila Kahwati: So, [inaudible], he is an employee of the manufacturer. He is a co-author on both studies. Both studies acknowledged [inaudible] in their acknowledgements, but there is not, at least in the first Insite publication, not a whole lot of information about exactly the role, but I think what you described is fairly typical of manufacturer sponsored trials.

Gregory Brown: Actually, I would disagree, and I think it's a common practice, but my experience when I was in academics was that your university would not sign off if you did not have complete editorial review and they could block your publication any way. So, anyway, I don't know what... I don't know this trial, what it was, but a well-done industry funded trial does not allow industry to edit and block publication until it's to their satisfaction.

Leila Kahwati: There's no other information. So, what you said is correct in the disclosures. David Share is listed as an employee. There is no disclaimer about the manufacturer having rights to review prior to publication. So, it's sort of a vague disclosure.

Gregory Brown: Yeah, but it, again, it's usually clear in the higher quality multicenter trials done that even when they're industry funded, that the statistician is independent and hired by, you know, usually the principal investigator at their facility and things like that so that there's a very clear separation

between the study and the company. This obviously does not have that separation.

Janna Friedly: That's my concern. There's no indication that there was any separation of data analysis and interpretation or oversight of the trial. They specifically said that the oversight was conducted by the company employees. So, it just raises... so when we look at, you know, with these color coded in terms of what the body of literature is, it... to me, it's striking that we have two studies that were, so it makes it look like there's more study, but really when you look at it, it's are they two independent studies or not? Is it really just one trial?

Leila Kahwati: It is two independent studies. The patient populations are different. They use a similar protocol. So, there are two studies. So, I think you might think of it as replication studies more so than one study. The...

Janna Friedly: The replication with the same biases and the same potential conflict. So, it, in my mind, it's hard to separate them. I'm thinking about what the concerns are about a trial. Yeah.

Leila Kahwati: And I will just note that source of funding is not a domain that's evaluated as part of risk of bias or a grade, which there is a lot of debate about whether it should be or not, but it is not considered in those ratings. And as I'm sure you're all well aware, there's clear evidence that with industry funded studies, especially when they don't have separation that the results are markedly different than studies that are funded at other sources. So, it definitely is something that's important to consider.

Seth Schwartz: I think a lot of that... it's real problematic that we're going on primarily an industry funded study, but then when we look at the effect size, it's pretty dramatic. When we look at the cohort study, the effects are even larger than what we're seeing in the randomized control trials, which is not atypical, but this variable effect size is in line with what we oftentimes see. So, I guess, while you guys rated the control... the cohort study as very low quality of evidence, I just want to be a little clearer on that in terms of, do you think this is a poorly done cohort study, or is it simply the inherent bias and that nature of the study design that's the problem here?

Leila Kahwati: It's the inherent bias of the study design, but it could have been done better. So, there was still, even with the inherent study design, there are things related to confounding that they could have managed better through their analysis and things related to selection bias that could have been done better. So, it's hard to call it, like, a bad study. I mean, we rated it using formal tools. So, it ends up as high risk of bias using our formal

tools, because there are aspects of it that could have been designed or carried out in a way that would have introduced less bias, but it would never rise above a low quality of evidence under the grade approach, unless we upgraded it for those reasons we talked about earlier. So, I'm just look... I just pulled it out to see, 'cuz I couldn't... I can't remember offhand. So, that cohort study was not... it did not involve the manufacturer, the Vanaclocha.

Chris Hearne: So, Austin, I'd be very interested in your... given your background, your perspective.

Gregory Brown: I'm sorry. Do we have... are we done with the questions for our contractor so we can let you sit down and get through our discussion?

Chris Hearne: Did I understand correctly that the adverse effect leading to a bilateral SI joint fusion was 8 out of 52, or 15%?

Leila Kahwati: 8 of the 52 participants received a bilateral procedure. So, at study entry, they had bilateral pain. They met the criteria to have a bilateral procedure. Now, it might have been sequence, like one side done first then the other. So, the rest of them only received a unilateral procedure.

Chris Hearne: So, I understood that to mean most started with a unilateral procedure that then progressed to bilateral.

Leila Kahwati: No. No. So, at study entry, people were either determined to have bilateral pain or unilateral pain. So, they received whichever intervention was appropriate to the pain. So, if they developed bilateral pain, that would have, I think, it was counted as an adverse event in one of the studies, but it doesn't necessarily mean it led to a bilateral procedure.

Chris Hearne: The other question I had relates to some of the conditions, specifically a single diagnostic block versus two. I saw that there were two different approaches with that. I also heard that you said that there was... that the second diagnostic block significantly reduced the false positive rate. So, is there information about what we know about the importance of that second diagnostic block in opening up the doorway to the fusion?

Leila Kahwati: So, the trial did not, they only used one diagnostic... I'm pretty sure they only used one. The experts who had written on diagnostic accuracy in the study that used two blocks, they see a lower prevalence of SI joint pain. So, it was because you have to score positive on both in order to be counted as having SI joint pain. So, it reduces both the prevalence estimates of SI joint pain, but it also just kind of raises the threshold to sort

of... it's another piece of evidence to say, this patient maybe really does have something going on versus just a false positive on a one-time block.

Chris Hearne: Do we know whether or not the conservative treatment addressed the perpetuating factors to the extent that they could be managed such as leg length deficiency or [crosstalk]?

Leila Kahwati: Yeah. So, I... they didn't really provide a lot of detail about the physical therapy. I assumed that most of those things would be addressed through the physical therapy component of the conservative management, but they didn't really describe specifically other than physical therapy tailored to the needs of the patients.

Chris Hearne: Okay.

Mika Sinanan: Is there enough information in these studies to say what the conservative therapy ought to be, or what the conservative therapy, that is, tried and failed ought to be? You just said that it's kind of all over the board. So...

Leila Kahwati: Yeah. I don' t think so, only because I think in order to draw a definitive conclusion about what it ought to be really would require testing alternative strategies and then seeing what works better. So, I don't think we can do that from this data.

Gregory Brown: Any more questions for our contract reviewer? Well, thank you, so much. It's a wonderful report. Okay. Then, let's start some discussion, and I think you had some questions for? We're gonna put you on the spot as a brand new committee member it looks like.

Austin McMillin: Well, my concerns firstly, I think that there is some good data and some ability to select patients properly into an SI joint fusion, obviously. The concerns that I have are on the upfront side, what's happening in the conservative setting that's leading them there, because my experience has been, in working with, on the manual therapy and rehab side for 30 years is that... and also in utilization review side where I'm reviewing records and analyzing what's been done is that conservative care can be all over the place and bouncing around here and there willy-nilly. So, it gets a little bit concerning when we don't really know what the conservative care is, and we don't really know what the test criteria are, the three out of five seems really soft to me. I don't know that we have any real idea about what the combination of those tests are. I saw six, and then we see three out of five. So, it's a little bit concerning about how we actually arrive at the point where we're driving the SI joint fusion other than to say, you know, the patient points to the area, which I think we all know is probably one of the

most sensitive things for the SI joint. So, that's concerning, but I think that it's important to take a look at establishing a threshold of having two diagnostic blocks rather than on as kind of a backup or a safeguard to preventing a false-positive on the first or establishing a pattern of relief from a diagnostic block, leading then to the fusion, especially since there is a risk of going into bilateral. I've seen that in clinic, and especially when something like leg length deficiency or gait change has not been addressed properly in conservative care on the upfront side, but then, the patient then lands in the SI joint fusion category, and then comes out with a leg length deficiency and the gait change is still there. So, I think that those things have to be kind of factored into the conditions if the fusion procedure is established as being something that would be covered.

Janna Friedly: I have a follow-up question to the one versus two diagnostic blocks. What's the evidence though about a single versus a double? How strong is that evidence to suggest that a double... looking at the analogous diagnostic blocks for facet joint conditions leading to RFA, the evidence is all over the place with whether you should do one or two and what the thresholds are, 50 and 80%, and any practical implementation of... did you get... in order to get a fusion, you have to have 50% improvement in your pain. So, if you have 50% improvement in your pain with a block... so there is a lot of confusion about how you actually implement that in a practical way. So, I'm curious about what the evidence is for one versus two.

Kevin Walsh: I'm sorry. I'm gonna interrupt. This is a discussion about coverage with conditions. What you're doing is talking about covering it with conditions. We usually start our discussion talking about what we think about the quality of the evidence and what that leads us to think about, whether we're gonna cover it or not. If we agree to cover it, then we talk about conditions. So, I would ask that we table this discussion until we get to the point where we've agreed that... we're kind of thinking we're going to cover it, and let's now get down into the weeds and talk about the conditions.

Gregory Brown: So, that being the question we're kind of talking about, is there enough evidence of efficacy to say that this is something that we should even think about covering. Is that what you're saying?

Kevin Walsh: I'm going to disagree with Seth. I have some really foundational concerns about the lack of specificity and the lack of control about conservative therapy. To say that these patients failed conservative therapy, when it seems that the range of conservative therapy meant good luck, see you later to a very maybe proactive prescribed multifactorial approach leads me to question the benefit that was demonstrated and if it would be as

real if there were multifactorial proactive conservative therapy over time that was of a quality that we would all find acceptable. So, because that is lacking, I feel that this evidence is suspect, and I am not impressed.

Gregory Brown: Maybe we can back up a second. So, one of the things I was thinking about is just internal consistency within this committee. So, I was thinking of degenerative disc disease and our decision to deny coverage for just pain. I mean, if there's instability, if there's fracture, or if there's something else, we would cover fusion, but for just pain, we did not cover lumbar spine fusion. So, to me, this is very similar, especially with the proposal from our agency directors, is that for posttraumatic causes where, you know, there is a clear injury and whatever, appropriate workup, and evaluation and treatment, failed conservative treatment, then we go, but... so, to me, again, if we're going to be internally consistent in our decisions, we're... are we starting at the... for pure pain, without some underlying cause...

Kevin Walsh: I respect what you're saying, but I think I'm trying to start this discussion a few steps back from that to say that just looking at the quality of this evidence, not whether our feeling about it is consistent with previous decisions, but just looking at the quality of what we have before us. I'm really uncomfortable that the benefit is real.

Gregory Brown: Well, so a couple steps back. So, are you saying, is sacroiliac joint pain a real... a unique individual entity? Is that...

Kevin Walsh: Oh, those have all... those are all interesting questions, too, because I'm suspect about the diagnosis in the first place, but I'm willing to grant that, Okay. Somehow or another this group of people got to the point where we were making this diagnosis. Then, we tried to separate them into a control arm and a treatment arm, and the control arm, again, as I just said, was kind of all over the place.

Gregory Brown: Alright. I think that's a perfect place to start, because again, part of the discussion is that there isn't a gold standard for diagnosis. There's a standard of what's considered to be met to say this is related to the SI joint. So, I mean, again, we can't even cover with conditions if we can't give a diagnosis to say this would be, this is the diagnosis and condition that we want to cover. So, let's start at that. I mean, do we think that this is a sufficiently defined diagnosis that we can treat it. Is that a better . . .?

Kevin Walsh: I think we're going to have to kind of accept the medical communities standard to say, this is being treated whether we agree or not. So, the question is, is this treatment supported by the evidence?

Gregory Brown: Well, so, okay. So, we're going to, we're all agreeing that this is a diagnosis. So, then the next step would be, how do we make that diagnosis? So, I mean, thoughts of what do you think is important to make that diagnosis? Dr. McMillin, Dr. Friedly, you certainly work in this area. When you see a patient, what is it that you do to make that diagnosis?

Janna Friedly: I think that's where I was going with the how do you... I think there are all sorts of concerns with how to define who meets the diagnosis that is treatable by this treatment. So, and I don't think there is a consensus about the physical examination maneuvers or the diagnostic blocks. So, it's difficult to come up with that set of patients that is most likely to benefit from this treatment, putting aside the concerns about the evidence, about the treatment itself.

Gregory Brown: But from a practical perspective, if we're gonna give a coverage decision to the state agencies, we have to come up with an operational definition of a diagnosis. Right? So...

Austin McMillin: Well, I'm a little bit uncomfortable projecting my personal clinical experience as the standard for how I would diagnose an SI joint. Right? So, I mean, there are certain things that I would do, and I've had experience with, and I think success with, but if we're actually looking at what does the research say, it's really not very good. So, yeah.

Gregory Brown: No, and again, the... this committee, every decision would be very easy if we had good evidence. They don't bring any decisions that have great evidence. They don't need our opinion on that. The evidence has already spoken. In terms of the evidence, we do have at least two RCT's that have inclusion criteria. So, they have diagnostic criteria there. If those are completely at odds with your clinical experience, then there may be some discomfort, but if in general they're pretty close, do we say 40%, do we say 70%... you know, 50%, 75%.

Gary Franklin: One of the confusing things for me in this is, yeah, you got your problem with, do they really have it or not from these tests, these non-objective tests. Then, you have the injection, but a lot of these patients had failed back surgery syndrome. So, how do you do the inclusion and exclusion criteria in somebody that got operated on in the first place with a fusion for chronic back pain. Now, they're coming in for another fusion procedure, and how do you separate that pain from the pain they had for getting the fusion in the first place?

Gregory Brown: Alright, I... again, it's one thing to say where the pain is coming from, and that's in the diagnosis. It's another thing to talk about coverage. Again, if

we say if it's only for traumatic or posttraumatic causes, then whether they've got... if they've got no trauma and they just have failed back, then it's clear where they are in terms of that coverage, but I think we need to start with what we think is a minimum criteria for a diagnosis.

Leila Kahwati: We did not include that kind of criteria in our proposal slide, since we were... since our recommendation was not to carve out a group within, that is covered, but we did, in case the conversation went in this direction, prepare some... an alternate proposal that has some potential criteria laid out. So, if you'd like us to pull that up for you to use as a starting point, we can do that.

Austin McMillin: Since any coverage with conditions determination we would make would be on the basis, primarily, of these two RCT's, then we would have to use the inclusion criteria that they use in those studies whether those are good or not. That's the only evidence that we have to work with is how I see it.

Gregory Brown: So, the Fortin finger test, what are the five provocative tests that they use, and then a response of at least 50% of pain improvement with a single injection? I think we can say the evidence of two is better. Again, that's... I don't think we're limited to only this, but I agree, that's a good starting point. I think image-guided injection is important. Go ahead.

Seth Schwartz: I think we're struggling with this stuff, but clearly these papers and this cohort study were able to define a population that they were at least able to show benefit in. Now, I think that... I completely agree with Kevin that I really struggle with the comparator, because I think that it's very unclear what was even done to those other people. When you select people who didn't get better with doing whatever was done and then say do whatever, they're not going to get better. So, that's kind of where we're biasing a little bit in favor of the surgery being beneficial. That being said, I think it's challenging because this condition sounds like it can be multifactorial in cause. Right? So, it can be a gait abnormality. It could have been an earlier injury. It could be a chronic use injury. It could be a lot of different things, but at the same time, if the common endpoint is that you have an inflamed joint, that if it's moving it hurts you, and if you fix it it's not hurting you, and we have evidence to show that if you fix it, it doesn't hurt as much, I'm having a hard time being super critical of that. So, anyway, we can kind of... we can massage this a little bit, but ultimately we have trials, we have data... relatively well done data. We can question were it comes from, but it's showing us that they were able to call out a population based on fairly defined criteria of patients who are gonna get better with this treatment.

John Bramhall: I think it might be futile to try and define conservative therapy over a constellation of patients, because I don't need to articulate it anymore. We will have concerns about the willingness of a patient to undertake physical therapy, the degree to which they participate in, the use of non-steroidals, the use of steroid injections into the joint. So, you know, all kinds of things that... so, to me, I just took a little bit more of a global view, in particular, with that Medicare financial data. So, it looked to me as if when the study looked at the Medicare financial data, which is elderly patients, I admit, but it's a constellation of patients, the cost of therapy was less in the population that had this intervention. So, what I did with that information was say, okay. You're dealing with a very variable group of therapies that are not the intervention and a sum total, whatever they did, which we can't pass out, was not as cost effective. I'm interpreting that as being clinically effective, and I don't know whether I'm... I don't know if I'm allowed to do that here by you guys, because I'm saying if it costs less, it probably was more effective. It's a little pragmatic, and it's one way into the conundrum of this unstandardized parallel treatment that we're going to try and use either as a gatekeeping mechanism or as a comparator for the intervention at hand.

Seth Schwartz: To piggyback on that, we're oftentimes charged with looking at extremely expensive interventions, I mean, multilevel lumbar fusion versus physical therapy is... you're talking about a multi hundred thousand dollar treatment versus this, which the cost estimate is a wee over $10,000 for this treatment. That's a different threshold that we're talking about. So, that struck me. The other thing that strikes me is that we're talking about these adverse events, but I'm not hearing about terrible safety concerns, really. None of the adverse events seem... we didn't hear any causes of paralysis or death or anything other than essentially some more pain, as far as I could tell. So, please vendors correct me if I'm wrong, but as far as what they're considering serious adverse events, they were fairly mild in the scheme of things, but in that setting, if we have something that's fairly ineffective, fairly inexpensive, seems to be cost effective, and is based on whatever loose criteria these studies have for us, seems to be clinically effective, and has fairly low risk, as far as I can tell.

Leila Kahwati: There were no deaths. The serious adverse events are events that do require hospitalization or medical attention, and that's what makes them serious, but I will caution that it's a fairly small denominator. So, it's... these studies, 102 in one and less than a hundred in another, they're not going to pick up rare serious events. You might have to treat hundreds and hundreds of patients and you might see a death. So, it's not a huge denominator, the trial evidence, I think, to make a definitive conclusion around the adverse events.

Seth Schwartz: But you showed us another trial that had 11,300 patients in it and showed a revision rate [crosstalk].

Leila Kahwati: Yeah, that's a database.

Gregory Brown: Dr. Franklin, you had a comment or?

Gary Franklin: Yeah. I think it's pretty likely that the most severe problems are pretty underreported here. We just happened to look on the Mod database, and I... and you saw some on a couple of slides here, but there were six reports from November 29th. I mean, this is passively reported. It's not an epidemiological study, but they were basically pretty severe... like, for example, they'll put in two to four of these things, and the adverse events is... the [inaudible] one moved and started matching on S1, and that's why they got the [inaudible]. L&I just had a case that you mentioned, I just found out about it yesterday, one that was put in, four that were put in and the patient ended up having to have an extended fusion beyond that by basically a trauma spine surgeon because it was so bad to start with, and the patient ended up with incontinence. So, I don't think we can say the consequences here are not severe. I don't think we know from these studies how severe they are.

Coner Kleweno: I'd have to agree with you, Dr. Franklin. I think that the risks of this shouldn't be understated. You will not necessarily die from the specific procedure, unless there is an anesthetic problem, or you will not become paralyzed in terms of the way you commonly think about it, but you are right next to the sacral nerve roots. So, it is quite feasible to have sacral nerve root compromise, which you mentioned. That can be whether it's sensory/motor, or bowel/bladder dysfunction, depending on how bad the complication is. Then, the other thing is, the amount of real estate so to speak, or the bone taken up by putting these in shouldn't be underestimated. Part of the reason probably the revision rate is low is because once those are in, if they're taken out, there's a huge area of bone that's no longer there to work with. So, that can be a problem for future outcomes for patients.

John Bramhall: Coner, when I've observed you doing this type of procedure, not this specific procedure, I've always been struck by how delicate it was and how much expertise it seems to take to put pieces of metal in this position accurately. That's just one other variable with the studies that we've looked at where, you know, I think the admonition from NICE is that it should be done by guys that know how to do it, which is yeah, but there is a variability, I'm sure, in the spectrum of competence within the

community of who could do this well and who can do it perhaps with a little bit more ambiguity. Would you, I mean, would you agree?

Coner Kleweno: I definitely agree with that. Where these are placed, as we know, is from the posterior ilium into the sacrum, and it's very uncommon for people to do that. It's most commonly done by a trauma surgeon in the setting of trauma. Now, there are spine surgeons that do go down and place fixation from the sacrum into the ilium for part of their fusion. I gather that, but the trajectory at which these are placed is uncommon for spine surgeons. These are placed in just a different trajectory that's dodging the vital structures in a different way. So, I would caution the utilization of this by people who are comfortable fluoroscopically guiding instrumentation adjacent to sacral nerve roots.

Mika Sinanan: Just a comment about the patient facing aspect of this. I was trying to envision it without the slides ahead of time. So, I looked up the procedure, and there is a whole patient facing set of websites that recruit patients and direct them towards physicians who are actually doing it, which speaks to both an economic benefit, an interest perhaps an expertise, but it also speaks to the bias that's inherent in the industry funded...

Gregory Brown: Expertise is going to a weekend course.

Mika Sinanan: ...but I mean, it may be volume. It may be that there are people who are volume. So, what my, one of my questions to you is, as you listen to this, did it match what you would have expected on the basis of your experience and the patients you are seeing? Or were there things that really stood out, and you said, the RCT's and cohort studies don't seem to match my experience?

Coner Kleweno: Thanks for the question. I have mixed feelings about this. I think that there is true pain of pelvic instability. I've done fusion procedures on patients carefully selected out. I have not put in iFuse devices, because I remain skeptical of the device and the potential morbidity of it. I guess I was surprised at how rereviewing the studies, the effect size, but again, that is in a setting of bias. I think the outcomes of people who have had it and are either still doing poorly or still have pain or have had recurrent pain, I think, has not been as aggressively reported. I think there are patients that will benefit from this when carefully selected. I think we'll all struggle with the criteria for selecting out those people. So, I think there is a true pathology in that area of the body that causes pain. Again, we are at a stage in medicine where we are doing relatively macroscopic procedures, driving large pieces of metal into very small areas, but I do think there are pain generators there that are real that can be helped by stabilization;

however, I am tempered on my enthusiasm, because I have a concern that there is a risk for overutilization without careful patient selection and an underappreciation for the risks and the patients who have received the procedure don't get better or get worse again, and there is not a great option for them.

Mika Sinanan: So, it's hard to back out of, once you've done it. Right? I mean, like you said, the undoing it or revision is a really complicated thing. It may create more problems. As you think about globally the technologies available or to be available for joint fusion, is this the way we are going to be doing joint fusions in the future?

Coner Kleweno: Great question. So, you see how there's not a lot of current data on open fusion. That's a much more invasive procedure that is... people who would do that are much fewer in number than people who would be willing to try to stick something in percutaneously. So, I think as we move forward, the technology will be percutaneous. Along those lines, I think that the research based on this shouldn't necessarily be held both positive and negative for emerging technologies for percutaneously SI joint fusion devices. So, this is a somewhat of a dowel that relies on bone overgrowing onto it, but it does not really adhere to the concepts or sort of precepts of joint fusion that we have done in orthopedics over time, which is joint decortication, autograft placement, compression across the joint. For example, if you fuse a knee or an ankle, all of those are sort of our precepts. This device is different; however, emerging devices are trying to address those concerns and address that kind of methodology. So, if the coverage is specific for a device versus a generalizable minimally-invasive SI joint fusion should be understood both for the positive and the negative, if that answers your question.

Mika Sinanan: Thank you.

Janna Friedly: Can I ask a follow-up question to that?

Gregory Brown: Actually, I'm sorry. I think we're...

Janna Friedly: I'm sorry.

Gregory Brown: ...I think we're getting off track, and I hoping we can bring this back. Kevin made a request early in this discussion. I'm not sure we've addressed that, Kevin. What's the first step... again, is the first step, do we have to operationalize to define what we're gonna do and then based on that say okay. With this definition, what's our evidence for outcomes and then safety and cost-effectiveness? Is that... so can we... I guess to me, can we

come up with an operational definition of a diagnosis that we're going to use to proceed, that we can agree on, because if we can't agree on that, I don't know how we move forward.

Mika Sinanan: So, I get back at Chris's point that we have to use the evidence, because we haven't looked at randomized control trials that look at the available techniques for defining the disease and how... I mean, we haven't. It's only within the context of these. So, either we start with that evidence, or we agree that the evidence is sufficiently imprecise that we can't actually define what the disease is, in which case we can't define who should get the treatment, and one of the reasons that I asked Coner that question was to see where in the continuum of evolving treatment for this we are. I think that was a very helpful description for me. So, we're not saying this is never going to be something that's an effective treated thing, but I think there's room for more precision in the definition of it in the future for both who would improve or who would benefit from it and who would not, and for the actual technology, itself. So, with that degree of imprecision, I really feel pretty strongly that Kevin is right on.

Sheila Rege: I wonder if we could similarly, go around the room with that question about is the evidence enough before we open it up to going another direction with the agency directors. I don't know where to start.

Laurie Mischley: I'm inclined to lean with the agency's recommendation. I mean, as I was reviewing this, I was kind of losing my mind over the lack of comparator group and just nothing to base it on. I couldn't help but appreciate that all of these people are failing conservative therapy, and there was something that they were reporting was helping them. Right? At the end of the day, in terms of advocating for the patient, it was hard for me to wrap my head around denying a procedure that was helping when nothing else was seeming to help. Right? And so, there's that side of me. Then, if I were... if I owned the company and I was funding a study, this is exactly how I'd do it, just conservative treatment... we'll leave it at that versus this well-defined procedure. So, I am so uncomfortable with how they've defined conservative that it is hard for me to appreciate the impact of the therapy. So, I kind of have to lean with where you guys are proposing.

Kevin Walsh: I think I've already said what I... how I see the evidence.

Gregory Brown: Well, I mean, just so I am clear. You don't think there's enough evidence to support this right now. Is that right?

Kevin Walsh: I'm so suspect about the way that these studies were done, that I doubt that the benefit is real.

Gregory Brown: Okay.

Tony Yen: I think that the evidence is actually quite weak. I think there is some there. I actually like how the vendor actually mapped this out with the evidence map. I thought that was actually very helpful, but instead of maybe perhaps the Insite and iMIA study being I think orange right now with moderate evidence, it'd probably be more weak evidence. I really liked how you brought out kind of the conflict with Dr. Share as the bottom line of him overseeing both studies and be involved in both studies, as well. So, I didn't recognize that. I think it's through this discussion here and also the identification of probably there's more publications than what's being reported that actually make me a bit more skeptical about if there's enough evidence to really say are we gonna approve this.

Chris Hearne: I agree with the general, I think Laurie said it really well. There's a lot of potential for bias in these two RCT's that makes me lean towards the agency recommendation. One thought I have on the topic of safety, if you're thinking that this procedure results in a 40-point drop in this visual analog scale, we know that even if there is some treatment effect with this procedure that that is probably inflated, because of the biases in the studies. So, if the true effect size is 20 or 10 points, or whatever, that changes the risk benefit analysis given safety concerns. So, I don't think we can... if the true effect size was a 40-point drop, which is incredible, then you would be well into tolerating the higher risk of harm, but given that that's probably not the actual treatment effect, even if there is a truer treatment effect, then we have to look at those risks of harms more skeptically, I think.

Janna Friedly: I would agree with everything that you said. I'm in agreement with those views. I also have some concerns about the lack of longterm outcomes and really understanding, especially in light of the fact that this is a procedure that can't be undone easily, what happens to these people five, ten years down the road. If you're doing this in someone who is relatively young who is postpartum, for example, what happens to these people long-term? That data just isn't, isn't available. So, we have emerging technology, potentially changing techniques. It makes me a little bit concerned about approving a procedure that may have unrecognized long-term risks.

John Bramhall: So, for me, the... so, just thinking ahead, the agency recommendation really excludes anything other than trauma or tumor. So, when I look at this issue, it seems to me like there's a real problem here. There's a biological problem. There's a constellation of descriptions of back pain.

We all know how prevalent this is and therefore how economically challenging it can be to treat with sophisticated interventions, but it seems to me there is a group of patients that clearly reveal themselves to have lower back pain, and they have a problem, and that problem needs to be addressed. Medicare and Medicaid in our state apparently covers this particular intervention. When I look at the problem of the diagnosis, injection seems a little problematic to me, as a naïve observer. I mean, I've done injections and diagnoses for axial back pain issues and radiculopathies. So, I know it's a challenge to interpret the results sometimes. Here, what we're saying is, one of the criteria would be an injection of local anesthetic and see whether you get pain relief. I make [inaudible] to where the steroids have been included in those regimens. I just don't know, but the point is, again, using common sense, not knowledge, common sense tells me that here if this SI joint pain is real, it's real, because it exists, is it secondary to mobility, to instability of an SI joint, or is it secondary to some other form or cause of inflammation. It would seem, again, to me, just from common sense, that there must be a group of patients who have inflammation that would then be responsive to injection but would not be responsive to stabilization, because their problem isn't instability. It's some other form of inflammation. So, it's hypothetical. I'm not going from the evidence before us. This is purely hypothetical, just in my own mind. So, the injection seems a bit problematic as a parameter, because it likely would identify a group of patients who do not have instability but do have inflammation. That's just a hypothesis of mine. Imaging is generally not particularly helpful in lower back pain. Right? I mean, that's just a... that's axiomatic. It just doesn't help a whole lot. So, you left with provocative testing, and you're left with the presence of localized pain. So, you come back to that original set of slides with someone pointing. Here's where it hurts, doc. I know it doesn't seem very sophisticated, but that seems to be where you land. Here's where it hurts, and then you say, well that's over the SI joint. Let's use some provocative testing to see if there is an increase in pain with axial or lateral or compression motion around this SI joint. So, I think that we would be able to have a diagnosis not as concrete as we would like to have, but a diagnosis, or a diagnostic root using the index finger of the patient and some provocative testing. Regarding the evidence, I'm impressed with the direction, the consistency of the direction of the effects seen in these studies. We come across this time and time again in this group. What we're looking for is very high quality objective data, and many times, we just don't have it, either because the studies were poorly done, they were done by a manufacturer and then we can't trust the results. They were done in ambiguous ways. This is our core difficulty month after month is the direction of the effect may be positive or negative and interpretable, but only interpretable if we're willing to overlook the inconsistencies in the

studies. So, in this concrete example here, I'm impressed, personally, with the direction of the changes, the improvements. So, I am impressed with the magnitude of the changes, and I acknowledge that the studies have been... they offer us weak support, not because the effect is weak, but because the study design to show the effect is intrinsically weak, itself. I don't know that we've successfully passed that problem as a group in the past with other sets of data, this distinction between the real effect being large or small or non-existent, and the way in which you demonstrate the real effect being inconsistent or weak. So, Kevin, I always hear your comments, because you usually raise this particular issue of the consistency and adequacy and believability of the data or the intensity of the evidence and support. And I completely agree with you, but nevertheless, I'm back full circle. You've got a group of people who are hurting, and you've got an intervention which seems, on the face of it, to have some benefit and, in fact, a lot of benefit for those people that were picked. That's why, as usual, I'm all over the place. I'm sorry.

Leila Kahwati: Can I actually just briefly correct you. I think you spoke, but this is covered locally under Medicare but is not covered under Medicaid.

John Bramhall: Excuse me. I misspoke. There were 44 states that sort of... not including Washington, but Medicaid. Correct?

Leila Kahwati: Yeah.

John Bramhall: Okay. Thank you.

Sheila Rege: I am... like, everybody else has talked about, struggling, because we're required to look at scientific evidence about safety and effectiveness, as the big keys, cost-effectiveness less so at the end. When I started reading and hearing, I mean, one of them, you know, they have nine authors in the Smith study, seven were employees, consultants, or stockholders SI Bone. There is another one where apparently SI Bone actually drafted the manuscript, and that just, I'm used to University studies, like, Greg said, where the funding happens. Then, the professors take care of it. I mean, you do the study and you report, perhaps give it to the company ahead of time so they are aware. So, the results... I think there is a problem. I don't think this is a made up problem, that there is SI joint pain. I just wish there was less bias in the evidence. So, given that our charge is to use scientific evidence, I'm not convinced we have that. I want to have that, because I do think our patients, and I think, especially our Medicaid population had that. I mean, there is a significant problem in our community. I would like to see better evidence before we make a coverage decision on it.

Gregory Brown: I get to play moderator and be last. So, Coner, I think it's important if you have a comment or, I mean, and if you say I agree with what's said, that's sufficient, but.

Coner Kleweno: I don't know if I'm repeating myself, but I believe that subtle occult instability in the pelvis is symptomatic, because I do pelvic fusions on the rare occasions, and I think that a micro-instability in the SI joint, as opposed to macro, which is what I see most of my practice in motorcycle crashes and car crashes. So, micro-instability in the SI joint can be symptomatic and can be helped with stabilization procedures. That being said, I also have significant concerns about the effect size, as reported by the studies that we were presented with, and I, again, think that there are concerns about the true potential adverse and safety effects of the device. Now, if the question is, do you cover 279, percutaneous, or minimally-invasive fusion, slightly different than do you believe this study by one single vendor on a procedure. So, back to your question, the way we will likely in the future address this problem is through minimally-invasive procedures to the SI joint. It's the same way that we converted in trauma, you know, 30 years ago. Everything would get opened up and fix a traumatic disruption of the SI joint. Now, we do most of it just percutaneous. There is a code for that that I use all the time, you know, 272.16 is percutaneous fixation of a traumatically injured SI joint. So, I think the charge will be challenging moving forward in not having as much comfort, in particular, in this refunded study, versus do we think that this procedural code will be of benefit to patients moving forward. I don't know if that's helpful or not.

Austin McMillin: I would mirror everything that's been said. I think that we've got some encouraging data, but it's clearly problematic with respect to bias. I think that we've got some problems with respect to how you diagnose micro-instability or if the pain is actually coming from the SI joint, some question about that. I think that it's encouraging that it's a low-cost procedure, apparently, with low risk. I was concerned with what Dr. Franklin said about under reporting, and it's been said elsewhere, as well, and I'm a little bit uncomfortable taking the Medicare population that shows lower lifetime costs, or lesser costs with a senior population that is less active and potentially sedentary and then superimposing that on a much younger population, but probably my biggest concern came from Dr. Kleweno, which said, when you said that it's an area for trauma surgeons, that a routine orthopedist doesn't normally do that. Opening up these procedures to just the treating public makes me a little bit concerned in that context.

Mika Sinanan: He looked at me, but it's him, right? We're not skipping Seth?

Seth Schwartz: I think Austin spoke very clearly and I feel quite similar, which is that, it seems that this is a real entity. It's unclear whether it's being over diagnosed because of our lack of quality... our ability to sort out who really has it versus who just has back pain, but it seems like a real entity, and there doesn't seem to be a good clinical alternative for treating these patients. This data is really problematic in the bias. We're seeing, I think, the effect of this is really... two industry studies is really problematic, but the effect sizes are impressive, and the effect size in the cohort study is being even stronger than the effect size of the randomized trials, which are not, by industry, is also impressing to me. I don't think I have a great handle on the risk of this procedure, and I think that's a little bit where I'm struggling, because this is a low risk procedure, I think even with our concerns about the data, looking at the cost-effectiveness issues, the [inaudible] problem, and the fact that there does seem to be something compelling here. It seems very useful, but if it's a high-risk procedure, that then... my standard or my willingness to offer this more widely is tempered considerably. So, I'm struggling with that, but I'm starting to be convinced that there is some real risk to patients who undergo this. So, there are some concerns about the quality of the trials rising up higher in that setting. So, I'm struggling here, because, well we rarely have good data. We very rarely have data that is this... that shows this degree of effect size with no contradictory data. So, it's harder to weigh this data in the setting of our concerns about it. They're simply on the way the studies were done and not that we're seeing conflicting results. So, that's a challenge.

Mika Sinanan: Emily and her presentation said that Dr. Franklin referred to the scale of the benefit as a miracle. I think that is in the setting of the limitations of the studies that we've seen, I think that you have to put the limitations of the study beside the potential scale or scope of the perceived benefit. As we've seen so many times before, industry funded trials like this always overestimate the size of the benefit. Either underestimate or substantially underestimate the risks associated with it. From an evidence based standpoint, I don't think we know what the basis for making the diagnosis is. I don't think we understand the safety profile, and I don't think we understand the full effectiveness of it. So, from an evidence basis, it would be very hard for me to justify doing anything other than what the agency has recommended.

Gregory Brown: I think your comments are spot on, Janna, and I... one of my favorite YouTubes is Ben Goldbaker in [inaudible]. I don't know if you've watched it. Basically, his comment in there is that industry funded trials are the best designed trials, and they can be designed to get the answer that you want. So, when they're designing the trial and employing the statisticians

analyzing the trial, and they have an exceedingly strong motivation to come up with the positive result, I can't believe it. I mean, I spent too much time with a mentor who has done it the right way, and they get industry funding, but then they go out and they design the trial, and they hire the statisticians, and they recruit the sites, and it's all done very transparently and above board, and there's a database, a monitoring board. There's no company involvement after... the company gets to see it, but they cannot edit it, they can block publication, none of those things are followed here. So, I guess I'm actually now struggling with, there's no evidence about posttraumatic SI problems. What evidence is there to support your recommendation, I guess, is where I'm currently struggling with.

Coner Kleweno: Exactly my question. I actually have two questions for you. Number one, you say posttraumatic injury of the SI joint. Does that means acutely, somebody gets in a car crash, and then this would be approved? Or does that mean they got in a car crash last year, two years ago, whatever it is, and have instability. So, I'm just, from a provider that would be billing for such procedures, I'm asking clarification on that. Then, secondly, if we talked about emerging technologies, would this be something that would be represented to the council if new technologies came out later? Okay.

Gregory Brown: So, basically how it works, if there is new evidence, then it can be brought up for rereview. So, absolutely, there's new devices, new trials, that it could be brought up for review.

Gary Franklin: Dr. Glass worked on our L&I policy, which is if somebody falls from a height, and then they have clearcut disruption of the SI joint on an MRI scan, and no matter what else is found, more or less, if you can demonstrate that trauma led to this acute disruption of the SI joint, then let the docs do what they need to do.

Coner Kleweno: But my question is why would you not use 272.16 for that? Why would you use, why would one use the fusion code? You typically treat trauma with fixation, not fusion, in this setting. It would be... I'm just curious as to how that came about. It's not unheard of, I would say, but I'm just curious.

Emily Transue: I don't have an answer. In terms of the coding, the decision is usually not specific to the coding. The playing out of how the coding would apply is done later. So, I think we want to look more at the language of the decision, and I think our vision was that whether it was done in that acute setting immediately or whether it was delayed with again a clearcut disruption, that either of those would be an acceptable use. I appreciate you bringing up the coding issue, because that hadn't come to our attention.

Coner Kleweno: So, if it's somebody two years out from a car crash that did not receive acute treatment, then it would be covered under this language, or?

Emily Transue: That would be our recommendation.

Gregory Brown: Even if they received acute treatment, I would think.

Emily Transue: Right.

Gregory Brown: With or without treatment, yeah. So, if there was a clearly traumatic event in their past. Yeah.

Emily Transue: And the committee is free, of course, to rearrange the way that's framed, as seems appropriate.

Sheila Rege: Should we look at that?

Mika Sinanan: We haven't reviewed any evidence to support any of that. Is that right?

Gregory Brown: That's what I'm thinking. Yeah.

Mika Sinanan: And that's your point.

Gregory Brown: Yeah.

Mika Sinanan: So, our coverage decision is really the second panel, page two of their recommendations, because that's the only evidence that we've looked at, not the first...

Sheila Rege: Can we pull the agency director recommendations out?

Gregory Brown: Well, I think we're getting a little ahead of ourselves. Can we… we should probably review our evidence.

Sheila Rege: Right.

Gregory Brown: Okay. I think we've done it informally in all of our conversations, but let's do it formally, and then bring up what you're saying. So, the tool on page five here in my book, safety outcomes, infection, serious adverse events, other surgical morbidity, revision surgery, blood loss duration. I think if I can summarize Dr. Kleweno, revision surgery around the sacrum is exceedingly difficult, just because of the bone loss, at least for this iFuse

device. So, you are, for lack of a better term, burning your bridges, and it's very hard to do some revision surgeries.

Coner Kleweno: I think that the revision surgery for this shouldn't be understated, and it's technically challenging dealing with bone loss.

Gregory Brown: I think the other safety concern is that, I heard from you, is putting in a sacroiliac screw or device, a fusion device, is very different than, let's say, a pedicle screw. So, an excellent spine surgeon, this may not be their typical approach and type of [inaudible].

Coner Kleweno: It would be less familiar with them, potentially, and taking all-comers, less potential, and the other question was about, oh, about the safety of revision. Interestingly enough, the worse the surgeon is at putting them in, the easier the revision probably is, because they're even further away from where they ought to be. So, there may be some bone socket left.

Gregory Brown: Okay. Are there any other safety concerns here that, I mean, that we're missing on the table in our tool here? Okay. I'm not seeing anything. Efficacy. So, our report came out with moderate evidence supporting improvement in pain, improvement in function on Oswestry, improvement in quality of life, and then we were told that GRADE has no way to include industry funded studies and upgrading or downgrading. So, the discussion I just heard was that we are downgrading those studies because of our very high concern about bias in an industry funded, as you would say, essentially one study not two. Is that a fair summary?

Janna Friedly: I think the other just methodologic concern, major concern that we all have with all of these studies, and it's also true of the observational study is that the comparator arm is people who have failed at the comparator treatment and then you enroll them in the comparator treatment, which they've already demonstrated to fail. So, you're setting it up in a way. So, it's not just the potential for bias, but it's the design of the study regardless of who funded it. That would be a...

Gregory Brown: Well, it's another form of bias.

Janna Friedly: ...another. Right. Yeah.

Gregory Brown: Okay. Any comments there? Do we agree there? Okay? Cost. Do we think there's any evidence on costs? I mean, there's some presented. Do we think it's biased enough to consider? I'm not seeing anybody...

Seth Schwartz: So, can I ask one question of our vendor on this one? For that cost-effectiveness trial that you guys looked at, what did they use for their effectiveness data in order to come up with that conclusion?

Leila Kahwati: So, it wasn't a trial. It was a modeling study. So, they used inputs from both iMIA and Insite trials.

Seth Schwartz: So, this is the data they used for effectiveness?

Leila Kahwati: Yes.

Seth Schwartz: Thank you. That's all I needed to know.

Gregory Brown: So, there is our cost-effectiveness or cost outcomes. Then, the next question is special populations, and this kind of gets into this posttraumatic SI issues versus other non-traumatic causes of SI pain. So, are we all in agreement, we have no evidence regarding posttraumatic causes of SI pain? Okay.

Coner Kleweno: I would just caution, that depends on if you mean, like, today you got in a car crash versus ten years ago.

Gregory Brown: So...

Coner Kleweno: In terms of posttraumatic. We have data that stabilizing...

Gregory Brown: ...how about chronic SI pain treated from a previous traumatic injury, I guess. Yeah. Is that more specific, but there are no studies looking at that specific subgroup or?

Coner Kleweno: Correct. There are no studies. We've not been presented with any studies with this particular device for chronic posttraumatic instability.

Gregory Brown: Right. There were some other case reviews or case control studies that were listed that were more observational. I know Woody Cross at Mayo had some of the publications. Mark Schlinkowski at the University of Minnesota had some of the publications. They are both trauma surgeons and certainly do it for that reason. Do we want to review them, as a way to get evidence, or is that not sufficient evidence to review? I guess my question is, if we're going to try and go with the recommendations from the agency directors, we need some evidence to justify...

Kevin Walsh: We're jumping ahead.

Josh Morse: In your binder, you have the key questions, but I am looking at the key question document and what was included or not. So, I guess I'd ask, Leila, did you look for anything beyond chronic pain?

Leila Kahwati: No, but our search would have found those types... the issue with acute injury, [inaudible] trials for that kind of treatment, because it's trauma and you just get the job done. So, I think [inaudible] is really on chronic SI joint pain and I would say that the inclusion criteria for the two trials, I don't think would have necessarily excluded somebody in a car wreck a few years ago that now has chronic pain. They didn't necessarily report those characteristics, but chronic SI joint pain was the criteria, not the etiology, per se. Does that make sense?

Coner Kleweno: And I think that's important to have that subset of patients with trauma and instability versus okay. I guess it's not the lumbar spine. Let's try the SI joint. I think that could be two populations that we have to be very careful that we're separating out.

Gregory Brown: I agree. That's what I'm saying. I'm looking for an evidence basis with which to separate them. So, I know, at least of the bibliography I reviewed, like I said, they were from WW Cross and Mark Schlinkowski and stuff, and did any of those case series, did they, since they're trauma surgeons, do you know if they focused on it?

Leila Kahwati: I believe they're all... all the ones we screened were all for chronic SI joint pain.

Gregory Brown: Okay. Okay. Well...

Josh Morse: So, if I understand the question, you don't have evidence for something beyond chronic SI joint pain. Your policy would be limited to that target, and anything outside of that would be left, that would be agency policy decision.

Emily Transue: Our screening of that decision was somewhat modeled on other policies. Our intent was to make sure that we didn't create a situation where we were looking at evidence around the chronic situation and sort of accidentally created a policy where we were saying that people couldn't get in for an acute instability, if that makes sense, or a tumor or the other circumstances. We were more trying to frame the second page of the...

Gregory Brown: Correct. So, I understand it's not... it wouldn't affect, again, like, Dr. Kleweno said, usually, you don't fuse for an initial trauma fixation or treatment, but in terms of someone with a traumatic cause that presents

two years later with sacroiliac joint pain, if we vote no coverage, that's no coverage and it would not be covered with this policy.

Emily Transue: Correct.

Seth Schwartz: But I would say, we do have the opportunity to have exclusion criteria, and one of the... we could designate as an exclusion criteria posttraumatic pain or something like that. I mean, we can massage that, but that would be an option.

Gregory Brown: Trauma, posttraumatic pain, whatever. Okay.

Sheila Rege: Let's ask the agency directors if that would be helpful if we did that, or just leave it alone and up to your judgment, like, is being discussed. What should the process be?

Emily Transue: I think you'd want to be somewhat more specific than trauma. We've all had trauma to our pelvis. I mean, I think just differentiating what degree of trauma would allow someone to fit into that category.

Sheila Rege: We had trauma, tumor, and I can't remember, two other things, sepsis and something else. I can't remember what it was.

Gregory Brown: And spinal fusions. Yeah. Well, so we... well, I guess the short answer is, is right now we don't have any evidence in terms of subpopulations to vote on.

Sheila Rege: So, what should we do?

Gregory Brown: Well, the evidence... we look at the evidence. We have to vote on the evidence.

John Bramhall: I have difficulties with the... not to jump ahead, but I have difficulties with this idea that you can separate the problem with the mechanism, and you're absolutely right. We all have trauma. So, if we were to go that route, then the way around it is to be able to claim traumatic injury seven years ago, ten years ago. So, there's a human factor element there. It seems like you're preparing us to think about well, are we coverage this at all for any reason. Then maybe we should make that determination here first, because in doubt is the data that supports the agency recommendation, because we've not been presented with it. So, we may finish up here saying this is an unproven technology, and it's not appropriate for any of the causes of SI pain, because we don't have the data. So, that would help us make a decision. We may go that route, and

that's a very... Kevin, that's a very pure route that Kevin would often advocate, but I don't know whether that leads us in the place that we need to be.

Gregory Brown: Well, I think...

John Bramhall: We don't have data for the trauma.

Gregory Brown: ...right. So, I think what...

John Bramhall: So, we need something...

Gregory Brown: ...I think we can be, you know, for example, if you got a chordoma in your sacrum and go in and resect that and end up needing to fuse some allograft to the iliac, you know, across the sacroiliac joint, we're not saying you can't do that tumor treatment by not covering this. So, we're gonna put... so, even if we don't cover, we're... what I'm thinking we're saying is, we're still not gonna include, we're gonna make exceptions for certain things.

Sheila Rege: Oh, but couldn't we just say SI joint fusion is not covered for chronic pain, which is what the evidence... that is what we asked our vendors to study, because it was considered experimental and investigational. That's what we discussed all morning. We didn't discuss anything else.

Gregory Brown: So, is...

Sheila Rege: And that...

John Bramhall: We didn't find that for chronic pain, this is an ineffective treatment. We had no data to say it was ineffective.

Sheila Rege: But it's a coverage. We're... it's a vote.

John Bramhall: Right.

Sheila Rege: So, in my mind, what I was listening to was the data on chronic pain all morning. I didn't listen to data on anything else, tumors, sepsis, infection. I didn't listen to any of that. So, if we just then end the morning, by the way, it's noon and we have to start the next one at 12:30...

Gregory Brown: You just want to get this chair, because you know I'm [crosstalk].

Sheila Rege: ...no. No. No. The evidence on chronic pain and limited to that. I mean, that's what we worked on all morning.

Josh Morse: Sorry to jump in again, but if you... just looking at the way we frame this, we have specifically excluded, thought it may have been caught in there, but the specific exclusion is recent major trauma or fracture, infection, cancer, or sacroiliitis associated with inflammatory arthropathies, listing specific exclusions that your policy that were designed to help you answer.

Sheila Rege: Right.

Gregory Brown: So, the trauma is already excluded.

Sheila Rege: So, we just say that and we put what was in there, and then we're pure. We're still pure.

John Bramhall: Sheila, just clarify. So, you're advocating that we make a decision on the basis of the evidence before us about chronic pain and the treatment with this either percutaneous or open fixation, and you're leaving on the table making no comment about the agency recommendation that these treatments be allowed for trauma. Is that...

Gregory Brown: If we vote...

Sheila Rege: Or we can...

Gregory Brown: ...if we vote no coverage, then their recommendation is irrelevant.

John Bramhall: Oh, is that right? Okay.

Sheila Rege: Well, we would put no coverage for chronic pain, and we would put in there, if we wanted to really be clear, the exclusion of what we [crosstalk].

Gregory Brown: Well, but it's already in there.

Sheila Rege: Okay.

Gregory Brown: So, it is clear.

Sheila Rege: Yeah.

Gregory Brown: Because it was excluded already. Yeah.

John Bramhall: Maybe I'm being dim, but then if someone is traumatically injured, ten years later presents with SI pain, they would be covered?

Gregory Brown: Correct, because it's already excluded in the way the question is asked.

John Bramhall: Well, but no, it's excluded from our consideration, but does that make it covered?

Gregory Brown: No. It means that it is, that this coverage decision...

John Bramhall: Does not relate to that...

Gregory Brown: ...is not related to that issue.

John Bramhall: ...so, they're gonna come back...

Gregory Brown: No. No. No. Then, the agencies can determine on their own.

Coner Kleweno: So, would that be under a different diagnosis? For example, I had a patient two years prior from South America, came up here, had a pelvic fracture. He had chronic instability. He had chronic pain, as well, but he had a clear pelvic deformity, pelvic instability. I open fused him. We want to make sure those types of patients who need it. I get the point of, yeah, 20 years ago I kind of fell on my butt down the stairs. So, that's different, but we would want to include people with real pathologies and trauma.

Gregory Brown: [crosstalk] lumbar spine surgeries.

Tony Yen: Greg. I would like to interrupt for just a bit. Can we just take a look at page #12 of our booklet, the bottom slide? I think that clarifies, and I really want to appreciate the agency recommendations over here. I think it clarifies a lot of this discussion, I believe. It's all already all clarified. The last side, and then the top of page #13 of our booklet, the first slide over there shows what agency is recommending in terms of including or excluding. I think this... we've been kind of discussing all these... I think that the components of these two slides. I think it outlines it fairly well. [inaudible] so we can actually kind of maybe clearly see it in print.

Austin McMillin: My concern is if the Labor and Industries discussion is really a 100 percent trauma based population, and we may be dealing with people that had remote trauma that got the ball rolling around the SI joint and I see patients all the time. They can't really remember what the event was five years ago, but I think that Dr. Polly brought something up that was important, which is that, you know, if you've got demonstration of loss in integrity of the joint, extravasation of fluid through the anterior SI, and to the ligament, then you've demonstrated a loss of integrity of the joint, which would then move you into a fixation model. So, I think separating

trauma, well this statement is, it's inclusive trauma and radiological evidence of joint disruption, but I think if you say or demonstrable disruption of the joint loss integrity, then that would qualify the patient to be able to go through fusion.

Coner Kleweno: And I agree with you, one caveat is if you're interventional radiologist is extravasating because they're not in the right place, or if there's an incompetent capsule, and that's an important distinction, because I think that there is a technique dependence of injecting into the joint, as you know, of course.

Gregory Brown: Okay. I appreciate your comment, Tony. I guess my question is, is just in terms of procedure, the way the question was asked for the report...

Tony Yen: Mm-hmm.

Gregory Brown: ...trauma is already excluded.

Josh Morse: Yeah. The way, I mean, not the way I read it, the way it reads is adults age 18 and over with chronic meaning greater or equal to three months, SI joint pain related to [inaudible]. That's the target for your policy.

Gregory Brown: Right. Yeah, but it's this... and at the same time, the excluded...

Josh Morse: Yep. It's right there, posttraumatic injury.

Gregory Brown: Right. So...

Emily Transue: We have the proposed language now posted. This is not the inclusion for the studies. This is the draft language.

Gregory Brown: ...so, to me it's cleanest if we say sacroiliac joint fusion is not covered for chronic SI pain, and excluded from that are patients less than 18, low pain of other etiology, SI joint related to recent major trauma or fracture, infection, cancer, other sacroiliitis, clear diagnosis of disruption, or diagnosis based on criteria other than those listed in the inclusion column. So, the way the question was asked is, let those exclusions stand. We vote no coverage for chronic SI pain.

Coner Kleweno: Or wherever you go. Yeah.

Gregory Brown: Or wherever we go, but I mean, those exclusions were still exclusions. Right?

Josh Morse: Yes. They are not on this [crosstalk]...

Gregory Brown: So, so...

Josh Morse: ...policy. Yes.

Gary Franklin: And, it would still be up to the agencies to implement appropriate criteria for the exclusions to allow them to get done.

Gregory Brown: ...right. Then we don't have to come up with a definition. We don't have to say what's appropriate conservative treatment. I mean, is that clear to everybody?

Mika Sinanan: I agree, and in addition, I feel like if you look at this, we have no evidence to say that iFuse is the right technology for any of those things. So, we would have to substantially change this.

Gregory Brown: So, we should go back then to our tool and we'll start with a straw vote on safety. So, and again, our comparator's question, so if we're comparing SI fusion, any technology, open versus percutaneous versus conservative treatment, is there sufficient evidence that the technology is safe for the indications concerned?

Seth Schwartz: [inaudible] conservative therapy, is that what we're talking about or?

Gregory Brown: Oh, no. Any, any SI fusion, open or percutaneous. Is it safer than conservative treatment?

Janna Friedly: I'm confused as to how to answer this question.

Josh Morse: These are challenging questions. These are non-binding votes on your percept-... your take on the evidence. There's a variety of options. Nine unproven, two less.

Gregory Brown: Efficacy, effectiveness.

Josh Morse: One more in some, ten unproven.

Gregory Brown: Cost outcomes and cost-effectiveness.

Josh Morse: It looks like ten unproven and one more in some.

Gregory Brown: Okay. So, those are all straw votes. So, we pretty much have a consensus, I think, here, unproven in all three. So, that being the case, if we're making

an evidence-based decision, and we're... the majority is saying everything is unproven, is there any option for coverage with conditions or coverage? If there is, anyone want to make a case?

Janna Friedly: I think it just depends on your terminology, coverage with conditions meaning the conditions that we're excluding or non-coverage with exclusions.

Gregory Brown: No. No. No. Again, the... we have to do it the way the question was asked.

Janna Friedly: Yeah, non-coverage then.

Gregory Brown: So, for... we are dealing with chronic SI joint pain, SI joint fusion for chronic sacroiliac joint pain, unspecified. Then, there are exclusions based on that, and those exclusions would then be dealt with by the agencies. So, any other comment or question?

Josh Morse: Do you want us to see what the inclusion/exclusion criteria are before you vote? We can do that if you like.

Gregory Brown: Well, we read them or we can... do you want to, or are we all good?

Josh Morse: Okay.

Gregory Brown: Okay. So, then our vote on coverage.

Josh Morse: I see 11 not cover. We need to check for Medicare and guidelines.

Gregory Brown: So, Medicare does not have any nationally. Locally, Noridian does cover the procedure, but I don't...

Josh Morse: It does not apply to the concern in regard to a national coverage determination.

Gregory Brown: Okay.

Josh Morse: There is not a national coverage decision.

Gregory Brown: Right. Okay. There are no... the other clinical practice guidelines, one was NICE. So, that, yeah, doesn't really apply to us, and it wasn't really a clinical practice guideline. It was a, what do you say, a treatment...

Emily Transue: Intervention procedure guidance document.

Gregory Brown: Okay. We need another acronym, huh? Okay. So, minimally-invasive SI joint surgery fusion for chronic, and that was NICE. The other one was from... is actually from an insurance arm. It's from... did you say AIM was from...

Emily Transue: They are a subsidiary of Anthem.

Gregory Brown: Anthem, so not directly applicable for us. So, I don't think there's any conflicting. Medicare does not have a national one, and the other two are... one is foreign and the other is an insurance company not a government agency.

Josh Morse: Okay. That concludes the first topic. Thank you, very much.

Gregory Brown: Okay. Thank you, everybody. So, just a question is another item that we have, and I don't know if we want to leave it until the end of the day, is our last tab. There's the evidence update on stereotactic radiosurgery and stereotactic body radiation surgery. So, do we want to talk about that while we're eating lunch so we don't have to stay at the end? Okay. So, let's get lunch, come back and sit down, and we'll talk about that. Then, I will just... an announcement. I am going to step aside as chair for the afternoon's topic. I do not have any financial conflicts. I am currently writing an article with some of the researchers of the American Academy of Orthopedic Surgeons on treating knee osteoarthritis with nerve ablation. So, perceived conflict or intellectual conflict or however you want to label it. So, Dr. Rege is going to chair this afternoon's session and that way I can participate and not try and moderate. I don't have a financial conflict. If anybody has a concern, I'm happy to step aside. It's just I'm almost an expert, but just for the knee arthritis part of it. So, I just... Josh and I had a number of conversations about that. Just for public appearances and like I said, if it's somehow perceived as a... I don't want to be going chairing the session. So, but if anybody has any concerns about that, I am happy to not vote. I mean, that's fine, too. Okay. So, let's get some lunch and come back, and we'll talk about this.

We've got everybody back here. So, if we're gonna do our working lunch, let's do the stereotactic radiosurgery and stereotactic body radiation therapy, the update. So, first, if Josh can just explain now we got to this morning.

Josh Morse: Yes. Sorry to interrupt your lunch with this, but this will save it from the end of the meeting. So, in the rules and the law for the Health Technology Assessment program, there is a provision for rereview. Anyone may petition the program, the director of the Health Care Authority who has

the authority to select topics, or you directly to select topics for rereview, petition you for that rereview. So, the process, people submit a form. We've received two forms in the past year requesting a rereview of this technology, the stereotactic radiosurgery and stereotactic body radiation therapy. Because the literature base for this topic evolves pretty quickly, and there are a lot of studies, it is not a simple matter to just look at those petitions and see where the new evidence is that might affect the policy, and that's kind of the question that's in hand. Is there new evidence that could change the previous policy? So, in this case, what we did is, we contracted with the center for evidence based policy to complete a formal update literature search. We did provide to them the evidence, the petitions to start from. Then they, of course, did a systematic search to bring this all up to date. The question that they're trying to answer is not will the policy change, but would the new evidence that they find, could it change their previous evidence conclusions in the last report? So, we were bringing this to you, required by rule that we consult with you, that the director consults with you for the potential for this to be reselected. So, we would like to know if, based on this information, if you think new evidence could change your previous determination. If you haven't already reviewed this, there is... I think the previous policy is described in here, and the bottom line assessment on page one summarizes what they have found, and we would ask for you to, if you feel you can weigh in today and provide that consultation to the agency and the director, we'd ask for that. Do you think this should be selected for rereview based on what you see here, or do you think there is not evidence that could change your previous policy, and we should not select it? We'll take that back through the topic selection process to the director.

Gregory Brown: So, if you go to the first page there, right under background, it says the Washington State Health Technology Clinical Committee commissioned an evidence review in 2012 on the effectiveness of SRS and SVRT for treating various cancers. On March 22nd, 2013, using that evidence review to guide the decision, the committee adopted the following covering decision. So, this is what they are. SRS for CNS primary and metastatic tumors is covered, a covered benefit for adults and children when the following criteria are met: [inaudible] functional status score, i.e. Karnofsky, is greater than or equal to 50, and evaluation includes multidisciplinary team analysis. So, tumor board, including surgical input. Then, SVRT is covered for adults and children for the following conditions when the following criteria are met: Cancers of the spine or paraspinal structures, or inoperable non-small cell lung cancer stage 1, and the evaluation includes multidisciplinary team analysis, including surgical input. All other indications are not covered. So, bottom line of the rereview is, they did not think it would change any of our recommendations. I'm an orthopedic

surgeon, and I would be the first to say, oncology is not my area of specialty. Dr. Rege that is probably closest to your specialty, and I don't know if you had sufficient time or comments or, anybody else, thoughts to... I'm putting you on the spot, but... they'd rather eat than talk, I guess.

Sheila Rege: Nomenclature SVRT is when you do treatments, five or less, and you kind of use certain equipment and five or less is in the U.S. In some other countries, they actually do eight treatments. There is a lot of research right now, even on things like prostate cancer where the patients come in for six to eight weeks on doing less, but it's... a lot of that is still in the research phase. So, I think this is something that new evidence is coming fast. We've covered the main things, which is CNS metastatic tumors and something near the spine, paraspinal inoperable lung. So, I think we've done what there's no controversy on. On the rest, I think we are going to get asked to look at it again, because there is research data that is... trials that are accumulating currently. So, I don't think it's there today. So, I tend to agree, but I must confess, I haven't done a search on what's out there right now. I kind of...

Gregory Brown: But it's not your job to do the search. That's what the contractor did, and they seem to think and, I mean, I look... I think kind of the key is, well what page was it, page six where you look at the number of trials, and the big numbers of trials, you know, three-quarters of them are in the brain and lung cancer in the top table.

Sheila Rege: ...the only one I see missing is the liver where we do SVRT, and most of them are metastatic. So, I'm not as worried, but there is the unusual liver malignancies, and Mika may have some opinion on that, too.

Mika Sinanan: The comparison was to other types of liver directed therapy and in the... I think that has to be customized on an individual patient basis so much that it's always the consequence of the tumor board, a discussion about the best options that include both case radiation therapy, when it can be appropriately targeted, proximity to major vessels, or either cryoablation or radiofrequency ablation and the thermal effect of that with blood flow close to it, prior treatment, amount of liver reserve. Those are all individual factors that have to go into it. Can I make a comment about the process of this?

Gregory Brown: Sure.

Mika Sinanan: I wasn't here when the original decisions were made. So, just thinking back to our last discussion, I think we can not only capture the decision, but we can capture perhaps a few bullet points about the areas of caution that

were raised, why we made a decision in a direction, and especially if we make a decision which is... that varies from what the agency recommendations are, because when we're looking at this rereview, the key questions are is the evidence changed in those areas of concern or caution, in particular. So, we could narrow the search a little bit, I think, or at least target the comments that we get back. So, the way the summary would go is, here's the summary. The previous areas of concern that were raised by the committee are the reasons that they chose a particular coverage determination or lack of coverage or conditions were, the new data does not address those, addresses those partially, addresses those completely and offers a different perspective. That would be very helpful to me, especially for new members coming on the committee who don't participate in the discussion. Of course, I'll bet you anybody who was around in 2013 isn't going to remember the discussion that occurred then. Josh, what do you think about that?

Josh Morse: I think it's a great recommendation. I do think what we attempt to do is very similar, just with some different language, because based on the requirement, which is, is there new evidence that could change your previous decision, and we have to walk that through what the independent vendor can do. They find evidence that could change their previous conclusions, which is presumably what you based your conclusions on. So, I think we may be able to do that.

Mika Sinanan: Well, their conclusions and the recommendations that are coming from the committee, which are based on that but also the agency recommendation and on our perspective on what the data seems to show us, because as you just heard, I think we had a different perception of what the risks were and what the efficacy was from a pure data driven, and that's in part driven by our expert opinion and our perspective on the industry funded studies, which was a bit different from what they said.

Josh Morse: We'll take that back and work on that.

Gregory Brown: My one question there is that to some extent, doesn't that require us to anticipate what the change may be? In other words, yeah, we have reasons for our decisions, and I think they're fairly straightforward, especially now that we tabulate our efficacy, safety, cost kind of concerns. We're unproven in all three for today's decision, but in others, it's, like, clearly, well it was an efficacy question. So, obviously in that, if there's new efficacy data then that's going to address what our concern was. I guess if we get more specific than that, like I said, are we trying to anticipate where future research is going to go, and if we are wrong, then

they could say, oh well, it didn't address that concern. So, no. There's no new data. Do you understand what I'm saying?

Mika Sinanan: I think it's a balance between the two.

Josh Morse: Just for more context on this specific one, the specific questions being asked by the petitioners is really to getting coverage for prostate cancer treatment, and that's a clear non-cover from your decision. So, we did ask for the entire search... we always ask, I think I can say that confidently, we ask for the entire decision to be searched again so that we aren't differentially updating the evidence. I don't know if that's helpful.

Mika Sinanan: I'm not saying we focus the search, but we focus... we can at least be assured in our minds that we're addressing the issues that were raised when we have thought it through after three hours of discussion previously. That's my point.

Gregory Brown: Based on that, if this is being driven by a question around prostate cancer, you know, the review says no systematic reviews, no randomized control trials on prostate cancer. There were comparative observational. Well, that's not gonna be strong enough evidence for this committee to...

Tony Yen: Greg, over here, the last page on page 23, it says there is one RCT that may be scheduled to be completed by end of 2020. So, one RCT and one non-randomized study. That's in the first paragraph. So, maybe not now, but kind of plan maybe for later. Is that fair?

Sheila Rege: I think it is coming. I don't know off the top of my head when the trials are finalizing, but that is an active investigation.

Tony Yen: So, maybe not this year but when the thing is actually completed and published. Is that Okay?

Female: [inaudible]

Gregory Brown: I guess my assumption is that if a compelling study comes out that whoever is interested in that is going to petition us again to say, can you rereview this. Something like this is just such a broad category with so many different cancers that are potentially being treated that, to... if the question came back as, would you reconsider for prostate cancer, that's a very different request than reviewing all of this. So, I mean, I can't predict, again, how it happened that... it doesn't sound like people are going to be bashful about requesting a rereview if they think there is new evidence supportive of something.

Josh Morse: We hope not.

Gregory Brown: Okay. So, are we comfortable making a decision today about... at this point we don't think there's new evidence to support a rereview?

Mika Sinanan: So moved.

Gregory Brown: Second? Any further discussion? All in favor of saying that we did not, there is not sufficient evidence for a rereview? Do we need a hand count on this one? I don't know. Any opposed? Okay. We're going to say you're 11 for and 0 against.

Josh Morse: Okay. Thank you.

Gregory Brown: That covers that.

Josh Morse: It does. Thank you very much.

Gregory Brown: Okay. And then, our schedule has us starting the peripheral nerve ablation at 12:30. Do we want to get right into that? I'll trade seats with you, or are you gonna...

Sheila Rege: I can sit here.

Gregory Brown: You're going to moderate from there. You got the hand microphone, so.

Sheila Rege: Yeah. I'm good. So, please feel free, and it's a good thing Greg is near me, feel free to help, as... because this is the first time I'm in this role. The only thing I would like to know. It's 12:50. I think that is the time segment we have to break for the phones and the public comment. I'd like to start by introducing our clinical expert, if you would tell us just in few sentences about yourself, where you're from, and your expertise, your practice.

Brett Stacey: My name is Brett Stacey. I am the medical director of the Center for Pain Relief, University of Washington, and a professor in anesthesiology and pain medicine. Prior to that, I was at OHSU in Portland for 18 years, and prior to that, University of Pittsburgh. I have treated joint pain for a long time and am interested in the osteoarthritis from the time of joint replacement and did some research looking at cost utilization prior to joint replacement and cost utilization associated with recovery after total joint stuff about eight years ago or so. I started going to meetings where people were talking about genicular blocks and genicular approaches, and I have been doing it for the last four, or more than that, I guess five or six years.

So, I have clinical experience. I see patients that come and are referred for that, and I have not done shoulder. I have done hip. I have certainly not touched the plantar fascia.

Sheila Rege: Maybe just for the clinical expert really fast, like me.

Mika Sinanan: Mika Sinanan.

Sheila Rege: I'm a radiation oncologist, as you just heard.

Janna Friedly: Hi, I'm Jenna.

Chris Hearne: Hi. I'm Chris Hearne. I'm a nurse practitioner.

Tony Yen: I'm Tony Yen. I'm a hospitalist.

Kevin Walsh: Kevin Walsh, family medicine.

Laurie Mischley: Laurie Mischley, naturopathic physician.

Sheila Rege: It's 12:49. Do we have to break for this open public comment, or can we have... start? Or what should we do?

Josh Morse: No. It would be best if the agency goes first.

Sheila Rege: Yeah. Okay. So, we'll have the agency go first. That would be really helpful.

Gary Franklin: So, I'm Gary Franklin, co-chair of the agency medical directors group and medical director at L&I. I have to say that as a neurologist, destroying nerves, this [inaudible] but this is a tough topic, because there's not much out there. We are getting increasing numbers of requests from a small number of doctors. It's not broad. There have been books written on this. There's a guy, I can't think, Delmore or something like that from Hopkins who would... there's not a lot of these kinds of nerve destruction procedures. We had a specific doctor in Eastern Washington that used to do these nerve ablation procedures in multiple nerves in various patients. So, it's a tough area. It's been a tough area for L&I, and we still get... one of the reasons we asked you to look at this is, we're still getting requests for it, and they are confusing. So, in spite of the evidence not being tremendous, but regardless, it should be looked at.

So, peripheral nerve ablation, this is for the treatment of chronic limb pain specifically. We're not talking about spine pain here at all. We're not

talking about the use of these procedures in regard to pre or perioperative or postoperative adjunct to treatment for surgery.

So, the kinds of nerve ablation you can kill a nerve in many different ways. Chemicals, surgical, cryoablation, thermal ablation. The idea is to destroy sensory nerves that might be transmitting pain signals. The types of technology reviewed in this report include pulsed radiofrequency ablation or RFA, continuous current RFA, cooled RFA, or cryoablation. One issue that I had wondered about is how well-defined is this anatomy, and this was one study that was sort of interesting where they looked specifically at the nerves innervating the anterior knee capsule with lots of variability in the trajectories and a lack of consensus on the number and origin of the nerves to the knee. So, it's just kind of something to keep in mind here.

The four ablation technologies are very different in regard to their design with approach, delivery, and proposed mechanisms of action, but they do all destroy nerves.

There are a limited number of published studies, 13 RCT's included in the effectiveness, then eight observational studies included in regards to safety. The RCT's include seven on knee pain, four on shoulder pain, and two on plantar fasciitis. There are no cost benefit studies. The evidence is essentially very low quality, again largely funded by these various device manufacturers. FDA marketing approval has only been achieved via 510K equivalence with pre-1976 devices. No PMA studies or more involved studies. Interestingly, all payers consider this treatment investigational. I can't remember looking at anything in this committee where it was sort of universally considered investigational.

The agency medical directors concern levels, safety this is what we thought originally, safety was high, efficacy was high, and cost was medium-high. I think I'd probably lower the safety concern to a lower level than that, because I don't know if there's a huge amount of safety information. There is one paper I saw and maybe Brett could speak to this. I don't know. It wasn't looking at ablation techniques. It was looking at what happens when you try to ablate a nerve or whatever perioperatively and these nerves are in neurovascular bundles and they was a pretty nice report on adverse effects after knee surgery when these things are done with knee surgery related to damaging those blood vessels. So, it's not pertinent to this specific topic, per se, but it is, again, something to keep in mind, if our expert could address that, that would be great.

Currently, the agencies don't really have a formal policy on this. So, it is probably covered [inaudible], nothing formal on this. There is not a lot of

utilization. You can see it's a pretty low number by the year in PEBB, both UMP and Medicare, pretty low numbers, and Medicaid and L&I. The highest average paid amount for whatever reason is in L&I with... this is per ablation, is $743, but in PEBB it was about $300. In PEBB/Medicare, we can't really get an accurate number [inaudible]. In Medicaid, it's around $120 to $150.

The key questions are, again, the same template questions that we have for every topic, so I'm not going to go over those.

In terms of effectiveness, the OHSU will go over this in detail. Grade is generally moderate to risk of bias on this with small study sample sizes, short follow-up, large or differential loss to follow-up, no RCT had adequate description of allocation concealment, and insufficient detail about co-interventions. Plus, there is a lot of statistical uncertainty, because there is... in none of these studies is there any adjustment for multiple testing, and no control for confounders. The strength of evidence is very low for RFA use for plantar fasciitis, and again, I don't want to go into the gory detail on all of this. The strength of evidence is also very low for chronic knee pain, but more evidence, of course. Then, pulse RFA is not better. This is one example where it's actually not even slightly better than the control arm in treating shoulder pain.

There is little evidence of serious harm in randomized and non-randomized studies. There were a few reports with serious adverse events or device malfunctions in the U.S. government databases. There is no evidence reported on cost-effectiveness.

CMS does not have a national coverage decision. We actually didn't check with the regional Medicare carriers on this, but on every other payer on this, it's pretty much all considered investigational and not covered. We didn't find a single commercial payer that covered this.

So, our recommendations on peripheral nerve ablation is that it is not a covered benefit for the treatment of chronic limb pain. Remember, we're talking about chronic limb pain. We're not talking about anything else. The rationale is the paucity of very low quality evidence, mostly funded by manufacturers, no endorsement by professional society guidelines, and no commercial payers who deem this technology cover it at all. It is considered investigational. However, the bright note is that there are 12 ongoing RCT's with various modalities for peripheral nerve ablation to treat pain in the knee, nine studies for the foot, one study for the hip, another study in post-amputation and phantom lower limb pain that are expected to be completed between 2018 and 2021. So, depending on

what you decide to do today, we can certainly rereview this when this other additional substantial information is available. Thank you very much.

Sheila Rege: You did speak fast. Thank you. Any questions for Dr. Franklin? Well, you got out of there scot-free there. We can open up the phone lines and have anybody here who was going to present? The rules are that if there are multiple individuals from one entity, we will be limiting it to five minutes total. Correct? And that's been communicated?

Josh Morse: Yes. That's what we've agreed upon.

Sheila Rege: Okay. So, please come forward and please let us know... introduce yourself, announce your conflicts if you have any.

Josh Morse: Over lunch, we did hand out a piece of paper from Avanos?

Sheila Rege: So, we all have this. Thank you for coming.

Anne Stefurak: Thank you. I appreciate it. Good afternoon everyone. It's a pleasure and an honor to be here. My name is Anne Stefurak, and I am in charge of Health Economics Reimbursement for Avanos Medical. We're the manufacturer of the Coolief cooled radiofrequency technology for the treatment of chronic pain whether it's spinal or peripheral knee and nerve pain. So, along with the fact, um, that Coolief technology is the only technology with FDA clearance to denervate [inaudible] tissue for the treatment of OA knee pain, Avanos, you may have heard, has also recently been selected as one of eight winners among 250 submissions of the FDA opioid addiction intervention challenge. Avanos is not only committed to conducting the gold standard trials necessary to report clinical and cost-effectiveness with non-opioid products, and we have many, but also innovating new ones. As for the AMA and many government agencies I'm sure you're hearing about, it is now critical, more than ever, for all to help remove barriers and support quality nonopioid alternatives in this opioid epidemic. We are well aware that pharmacological therapies have significant risks that affect all areas of life, both short and long term. One thing, though, there is a lot of confusion about cooled radiofrequency, there's the assumption that it's low thermal, or it's cryoablation actually, it's just an optimized version of conventional radiofrequency. The water coolant probes, what they do, they place them at tissue charring, but the technology actually denervates [inaudible] greater than 83 Celsius, just like conventional. This has actually been reported through preclinical published literature, as well as supported by four medical societies. Economic studies are on the way. I know you're looking at them, as well.

An economic study poster that was presented at the ASRA April 2018 conference last year resulted in greater quality adjusted life year gains at six and twelve months versus steroid injections. That's per the date of study. As a U.S. 100k/QALY threshold, cooled RF has an 86% probability of being cost-effective at six months and 95% at 12 months. Some medical societies do support this procedure, specifically [inaudible], and cooled RF has a long history of safety whether utilized to ablate a liver tumor, treat an arrhythmia, or ablate a genicular nerve. In summary, we have found our patients find and our physicians find that it really does work. Just FYI, in terms of Noridian per the LCD 35456, effective of 10/1/2017, titled nerve block actually includes thermal RF as being covered for OA knee pain. Thank you.

Sheila Rege: Thank you. Questions?

Mika Sinanan: May I ask a question?

Sheila Rege: Well, that would take them to their five minutes. So, can you wait and ask it after they've all presented. There are multiple people from the same company.

Mika Sinanan: Okay.

Sheila Rege: I just don't want to go over five minutes. Go ahead.

John DiMuro: Good afternoon. My name is John DiMuro. I have a disclosure with Avanos. I have been a researcher with them, unpaid, and I have served as a cadaver proctor for Avanos. I am here to discuss the Avanos medical cooling system for peripheral joint radiofrequency ablation. I am board certified in both anesthesiology and pain medicine and the former chief medical officer for the state of Nevada. I have also served as a physician clinical reviewer for NIA Magellan Healthcare and continue to serve as a subject matter expert for the city of New York regarding medical issues stemming from the 9/11 terrorist attacks. As one of your original researchers for Coolief back in 2005, I have used the Coolief products longer than anyone in the world. It is amazing to see that our original research on this product has developed into a global standard for not only spine pain, but even more common pain syndromes in the peripheral joints, including the hip joint and knee joint. Avanos has made it a priority to educate medical providers about best protocol and ease of use for its product line. I have served as a lead proctor for many cadaver courses for more than a decade demonstrating the simplicity and rationale for this innovative modality. While I will not wander down a rabbit hole explaining the details of the protocols, I will tell you that the technology and ease of

use for the Avanos cooling system will make a good doctor a great doctor. Published studies and cadaver dissections have clearly demonstrated the [inaudible] superiority of Coolief for radiofrequency ablation over conventional radiofrequency ablation. As the former chief medical officer for the state of Nevada, I am intimately familiar with state-revised statutes, rules, and regulations. I will tell you that the State of Washington will actually save money by approving use of this modality. The use of Coolief will help decrease pain for not only repeat procedures but also in turn reduce costly analgesia and opioid consumption. As a cowriter for Nevada's opioid bill in the 2017 legislature, a bill sponsored by Governor Sandoval and approved unanimously by the legislature, I can tell you that inadequately treated pain syndromes account for a significant number of cases of opioid dependence and subsequent increases in both mental health and substance abuse spending. As the former peer-to-peer reviewer for Magellan Health where I provided thousands of reviews of medical cases requesting medical coverage, I was able to quickly approve these treatments after a simple review of the medical literature from even a simple Google scholar search. Today...

Sheila Rege: If you could finish. We're at five minutes already?

John DiMuro: ...sure. I have reviewed the final evidence report from the Health Technology Assessment program. Documented in that report is the dismissal of published evidence due to possible investigative bias. In order to dismiss the studies from a scientific viewpoint, the Health Technology Assessment would have to refute two well-established medical facts. One, that the knee joint is innervated by the genicular nerves, and two, that radiofrequency ablation is an effective tool for denervation. Fortunately, the medical community has no disagreement about these facts. The typical algorithmic workup for knee joint pain includes physical therapy, medications, several injections, intraarticular hyaluronic injections.

Sheila Rege: You're over a minute over. So, I am going to have to have Dr. Sinanan ask his question.

John DiMuro: Absolutely.

Sheila Rege: Thank you.

Male: [inaudible].

Sheila Rege: Yes, please use the mic and identify yourself so we can... we have transcripts made of our meeting.

Anne Stefurak: It ranges approximately $4000 for the capital equipment.

Mika Sinanan: Thank you. And the per procedure cost?

Anne Stefurak: Per procedure costs... the reimbursement, Medicare reimbursement in a hospital outpatient center is approximately $1600, and the [inaudible] is approximately $100, and the [inaudible] reimbursement is approximately $300.

Mika Sinanan: And you said ASC and in-hospital? Is it done either in an ASC or a hospital operating room, or in other procedural areas?

Anne Stefurak: For the knee, the majority of the time, it's done in the hospital outpatient center. It can be done in an ambulatory surgery center currently. They use fluoroscopy.

Mika Sinanan: So, the anesthesia is local or regional or sedation? I'm just...

John DiMuro: This is Dr. DiMuro. I can answer that question. It can be done under no sedation, which I do primarily in my office. It can be done under intravenous sedation or general anesthesia.

Sheila Rege: Any other questions? Should we see if the lines are open and see if we have any other...

Brett Stacey: Real quickly about the capital cost of equipment. I don't think many people buy the equipment to do cooled RF for the knees. They buy the RF to use for all the different things they do RF for. So, that is... one device does all the radiofrequency.

Sheila Rege: Thank you members of Avanos. Is that somebody else from another? Great. We'll have you present. Thank you.

Diane Jackson: Hello. My name is Diane Jackson. I'm here representing my mother who is Joanne Jackson. Joanne is 88 years of age. She has dementia, and she has GERD, and she has osteoarthritis, especially on her knees, which are bone on bone. She started exhibiting pain in her knees at the age of 77. Hindsight is always 20/20. We should have had her into knee replacement at that time, but now with her advanced dementia, that's not an option. My mother, when standing would say, I can't stand the pain. I can't stand the pain. Please, God, why do I have to suffer like this? And as a daughter, I felt that I needed to find something to help my mother, and I went down a very long, long and roundabout journey. That journey included everything there is to do for knees, including physical therapy. It included

massage. It included heat and cold. It included cushiony soles on her shoes. It included... I have a list. I had a PowerPoint presentation, but I didn't bring it soon enough. Certainly, Tylenol, naproxen, the results of those with the kidney and the liver and diclofenac sodium gel on the knees. I tried knee braces. She wouldn't wear that. Lidocaine patches, those made her severely confused. She actually went into a state of delirium and those had to be stopped. Narcotic pain medication was not an option, I think, especially for the elderly. They're at high risk for falling and also they would result in a lot of confusion and that was simply not an option. We tried stem cell treatments. Joanne walked until she had a very severe [inaudible] multiple trauma illness, and that was in December of 2015. It took her nine, she walked until then. She had pain and in September of 2014 actually had stem cell treatment done derived from fat, and that was very successful. She walked until that very traumatic illness she had, which was very inflammatory. Is my time up? Pardon.

Sheila Rege: One minute remaining.

Diane Jackson: Anyhow, so after her illness, the benefit of the stem cell treatment was gone. We tried stem cell treatment with blood throughout after her illness. That had no effect at all. So, then, I looked further what could be done, and she went this a roundabout way. We got to Dr. Jung Woo at the University of Washington Medical Center. He [inaudible] her right knee and her left knee with peripheral nerve ablation. She was ten plus, 13 plus out of 10 with pain before. I would give her a 2 out of 10 now, and probably that's because she has a contracture in her muscles from sitting in a wheelchair for five years. She was wheelchair bound after her illness. So, it worked.

Sheila Rege: Thank you. If you could, for the record, tell us your name and any conflicts, that means even if somebody has paid for your trip here or anything?

Diane Jackson: No. No. No conflicts. I took four hours to come here.

Sheila Rege: And your name for the record?

Diane Jackson: Diane Jackson.

Sheila Rege: Diane Jackson, thank you. Thank you, very much. Anybody else here or on the phones? If not, I think we can move on to our evidence report.

Valerie King: Good afternoon. I'm Valerie King from the Center for Evidence-Based Policy at Oregon Health and Science University. I am a physician and epidemiologist there.

I'm going to follow a fairly standard format here starting with background, talking about the methods we used on this report, the included study, giving some detail about that along with the results. We will give you a GRADE evidence summary. Sorry, not an evidence map, but maybe we'll do that next time, and also talking about the clinical practice guidelines and the payer policies. Then, finally, a set of conclusions.

So, as you all are incredibly well aware, there are many causes of limb pain. The chief among them arthritis, mostly osteoarthritis, but some other kinds, as well, but also traumatic injuries and soft tissue types of pain related conditions. The treatments really range from lifestyle intervention, such as weight loss and physical activity, certain kinds of medications are often used, physical therapy modalities, complementary and alternative modalities, including massage and acupuncture, and then all the way ranging to surgery in this area generally joint replacement.

As Dr. Franklin told you, peripheral nerve ablation destroys sensory nerve tissue. There are some different kinds of nerve ablation that are used, and he covered that. The ones that we'll be talking about today are conventional, cooled, and cryoablation.

Just to give you a little bit of orientation to anatomic areas that we're going to be talking about, although there may be a little bit of controversy about exactly where the sensory inputs to various joints are, I will say that the studies, particular of the knee, are pretty consistent about the targets that they use, and those are the superior lateral, superior medial, and inferior medial genicular nerves. The one that you will not see is the inferior lateral, and that's because of concerns of that particular anatomic area by motor nerve damage.

At the shoulder, a much less colorful picture, the thing you need to know about the shoulder is that there is mixed sensory and motor innervation at the shoulder and the kinds of radiofrequency that are done there are generally done through the suprascapular notch and are done with pulsed radiofrequency, which is probably less long-lasting in its effect, but also less likely to damage motor neurons. There are some experts that consider pulsed radiofrequency to be ablative, and others that consider it to be neuro-modulatory, but in either case, we do see evidenced in review articles that these types of procedures do eventually need to be repeated, even the ones that are done with ablative techniques.

These are generally done in procedure rooms, operating rooms, depending on the setting and sometimes even in office space settings. They are

conducted under sterile conditions. The picture on your left shows radiofrequency cannulae that are inserted into the knee, and then you see wires that are going to the radiofrequency generator. Peripheral nerve ablation procedures are often conducted with fluoroscopic guidance. That's really true of the knee. This picture just shows that fluoroscopic x-ray picture.

As Dr. Franklin told you already, the radiofrequency techniques do vary a bit by temperature, but also by the treatment area, and I think one of the things that Dr. Stacey is going to tell you is that although cooled radiofrequency is somewhat similar to conventional radiofrequency ablation, because of the water cooling and because it then prevents charring, that it allows the treatment of a wider area. With cryoablation, that is the use of a cryogen. So, think liquid nitrogen. That actually damages the nerve because it gets too cold instead of too hot.

The FDA does not really regulate these procedures. They're medical procedures. So, they are done with devices that are regulated by the FDA, but all of those devices are really ones that have received section 501K premarket approval by the FDA and not on the basis of studies of those particular devices, but only that they are comparable to prior approved devices. There is a list of the kinds of manufacturers that we found in the evidence review.

Dr. Franklin really went over this already, the population for the search was adults and children with chronic limb pain, peripheral nerve ablation by any technique was the intervention, and we were willing to accept any type of comparator, including sham and placebo. The primary outcome is function and secondary outcomes were pain, use of subsequent interventions. We looked broadly at harms for safety and were willing to take almost anything on economic outcomes, cost-effectiveness studies, cost studies, anything.

The key questions you have in front of you and were also shown by Dr. Franklin. So, we will be going over this in terms of evidence of efficacy and effectiveness, evidence of harms, evidence about whether there were any subgroups of distinct populations that might be more benefited or more harmed by these interventions, and then economic outcomes.

In terms of eligible studies, we looked primarily for randomized trials for any of these key questions. We also accepted non-randomized and non-comparative studies for questions of harms or harms to a subgroup. For cost-effectiveness, we were willing to accept randomized trials, systematic reviews, modeling studies, really almost anything.

We conducted an Ovid Medline search with specific strategies in Appendix A of your report. We also looked at the Cochrane Library, not only for systematic reviews, but at their central register trial. We looked at additional sources of evidence for really evidence reviews, technology assessments from the Agency for Healthcare Research and Quality, UK's NICE program, the VA's evidence synthesis program. We also looked at referenced lists of included studies, and we looked in public comment when we received a study that we had not previously identified. We evaluated it, as well. We did dual independent inclusion at all stages.

Then, beyond that evidence review, we looked at ClinicalTrials.gov database for ongoing and recently completed registered trials. We took their NCT numbers and then went back to Medline to see if anything had been published. That was not true in this case. We looked at the FDA's Manufacturer and User Facility Device Experience database, affectionately known as MAUDE, and the Medical Device Recall databases from the FDA, as well. These are for adverse events reporting. For clinical practice guidelines, we got in under the wire and were able to do a search of AHRQ's National Guideline Clearinghouse before it went bye-bye. Then, we updated that and looked, as well, with Medline search for guidelines. For payer policies, we did your standard ones that you like to look at, including CMS, MCD, LCD, and your interest... your three private payers of interest.

After all of that, we looked at 2376 citations. We assessed 259 articles in full text, and ultimately included 21 studies; 13 randomized control trials, and 8 non-randomized studies that were included for safety only.

We dually independently assessed risk of bias using instruments that are ones that we have adapted from some of the used instruments that are used internationally, giving you a rating of high, moderate, or low risk of bias, and I will just tell you, as opposed to the way the instruments that RTI uses to do risk of bias assessment, we do include financial conflicts of the study funder and study author levels, as part of our assessment of risk of bias.

We also use the grade system. Again, this ranges from very low where we essentially have no confidence in the estimate of effect for that outcome, all the way up to high where we are quite confident that the estimate of the effect is really likely to be true.

There are a lot of scales used in this field to assess pain and function and all kinds of other things. So, let me just give you the crash course here.

We'll talk about knee function first. First of all, in any scale, you have to think about... there can be a difference, but is that a clinically significant difference, or is it just a statistically significant difference. So, that term about whether it's clinically significant or not is called an MCID, or a minimal clinically important difference. A rule of thumb is that in general an MCID is about 10 to 20% of the value of the scale. So, if you have a scale that goes from zero to 100, the MCID is likely to exist in the range between 10 and 20 on that scale. That really changes, though. What I would say is when these particular scales are used for knee replacement or for assessing knee pain from osteoarthritis that can be quite different. So, using them in a surgical context, using them in a post-trauma context, can change what the MCID is. So, just with that caveat. The two major functional measures at the knee that we looked at in and were really reported in the literature were the WOMAC, which is the Western Ontario and McMaster Universities Osteoarthritis Index, which is why the call it the WOMAC. The MCID on that scale is between 10 and 15 points. The WOMAC total, which assesses function, stiffness, and pain, all three components, ranges from scores of zero to 96 or zero to 240, depending on whether they use a four-point scale or a ten-point scale for the subs. Lower scores on this particular instrument represents less disability, less pain. The OKS is the Oxford Knee Score. It's a self-administered questionnaire. It's got 12 questions. Each of those are scored, and the total therefore ranges between 12 and 60. Again, lower numbers representing better outcomes. The MCID on the OKS is between 6 and 14 points.

Mika Sinanan: Can I ask you a question? Your comment about the minimal clinical important difference, the MCID, difference in surgical context or knee replacement? I don't understand why it should be different. Should it be smaller or bigger?

Valerie King: It's just different.

Mika Sinanan: Is it a different score?

Valerie King: No.

Mika Sinanan: Where you would expect a different value?

Valerie King: You expect a different value.

Mika Sinanan: And is the value different bigger or smaller?

Valerie King: It depends on the body area and the clinical situation.

Mika Sinanan: Well, for knee function?

Valerie King: For knee function let me start with a different example. If you have really, really horrible, awful knee pain, you're disabled from it, it will take more of a change for you to be functional. So, the MCID, when you start at baseline with really, really horrible knee pain, it's higher. So, the MCID is higher in those situations.

Gregory Brown: I'm sorry. That's counter to the concept of an MCID. So, my review of the literature is that... what I've seen [inaudible] is a five for the Oxford Knee Score. Actually, I had a patient where the outcomes [inaudible], and it depends on how you calculate if there's patient weighted... where they have to remember what it was before. So, there's a bias on the patient's memory. There's statistical methods or distribution methods and calculating it that way. It was 4.5, so within 10% of the other estimate. So, I've never seen 10 to 15 for MCID for... or I'm sorry, 6 to 14 for [crosstalk].

Valerie King: Yeah, it's all referenced in the report. What I will say is that we looked for MCID's that were non-surgical.

Gregory Brown: Okay.

Valerie King: So, the MCID for knee replacement is different than the MCID for joint injections, for example. So, we tried to pick MCID's that were comparable to the patient's situation, and since none of these people were having surgery, per se, we picked numbers that were the most comparable based on usually systematic reviews at the MCID levels.

Mika Sinanan: I don't want to belabor this, but just to narrow that example you gave, would I expect the MCID for pain at the measure for knee injection versus a knee replacement? Which one would be a higher range? What's the target range? Is it higher for the knee replacement or for the injection, or does it vary?

Valerie King: It varies. So, baseline pain matters, the function and ability of the person, and the other things that they do in their life matter.

Mika Sinanan: Let's say it's the same patient. So, you haven't changed the patient.

Valerie King: Dr. Brown is absolutely right. I missed both on that example. So, if you're having a knee injection, probably overall you're at less baseline pain than if you're having a knee replacement, probably.

Mika Sinanan: [crosstalk] difference.

Valerie King: Let's make...

Mika Sinanan: You're not expecting as much of a difference.

Valerie King: ...let's make that assumption. So, if you are pretty functional and your knee pain is fairly moderate, and you've gotten an injection, we would expect that for you to notice the change, there will need to be more change.

Mika Sinanan: Alright.

Valerie King: If you just had a knee replacement, you may appreciate a difference in pain once your wound is healed and all of that, you may feel a bit better with less of an improvement compared to the injection person, but again, this really does vary. It's a completely confusing body of literature, and systematic reviews have been done on lots of this. It's very complicated, statistically complicated with statistical methods used change the MCID, that sort of thing.

Gregory Brown: I think you're confusing minimal clinically important difference versus expected outcome. In other words, the minimum clinically important difference is the minimum, essentially minimum clinically important change that your patient can notice, but if I'm going to take an Aleve, or if I'm going to have my knee replaced, I expect a heck of a lot more improvement from the knee replacement, than I do from the Aleve. So, I think... so, in other words, I would... the work we found is the average was at least three MCID's for a knee replacement in improvement. That was the average. So, 90+% had at least one MCID, but hopefully, if you're getting a knee replaced, you get more than a 1 MCID, but again, I think you're mixing the two, yeah.

Mika Sinanan: No, but that's helpful. That was... the way it was said, it was counterintuitive to me, but that helps. Thank you.

Valerie King: At the shoulder, the most common scale is the SPADI or the shoulder pain and disability index, and that is a scale that goes from zero to 130 with lower scores being better. The scale for function for plantar fasciitis that we saw in the literature was the AOFAS, the American Orthopedic Foot and Ankle Society score, and it has both function and pain components to it. It also tracks on what the foot's alignment is and rates that. The total score range was from zero to 100, and compared to the other functional

measures that we looked at, this is the one where a higher score is better. For all the others, a lower score is better.

Then pain also has its measures. The most common one that we saw across studies is the visual analog scale or the VAS. This is a continuous scale that goes between zero and 10 or zero and 100, depending on the scale that's used. The endpoints of that scale are anchored with extremes, and you had this administered to you probably where zero is no pain at all and 10 or 100 is as bad as it could possibly get. The NRS is really similar to the VAS in reference to a numeric rating scale. And the difference here is that it's an ordinal scale. So, there aren't points on that scale between two and three. It's either two or three. On the VAS, you could be a 2.5. So, zero, again, is no pain and 10 is unbearable pain.

So, with all of that preamble, let's turn to the evidence review. For key question one on effectiveness, there were, again, 15 randomized trials. We have evidence only for knee pain, shoulder pain, and plantar fasciitis. So, that leaves a lot of limp pain that's not covered by randomized trials at this point in time. There were five conventional RFA knee studies, one cooled, one cryoneurolysis. The four at the shoulder were all pulsed radiofrequency, and for the plantar foot, there was one of conventional RFA and one of pulsed RFA. Eleven of these RCT's were rated as having a high risk of bias. Two of them were rates as having a moderate risk of bias. Those two are the one of cooled radiofrequency at the knee and of pulsed radiofrequency at the foot.

I'm going to go first to the knee, then to the shoulder, then to the foot, and in the knee, I'm going to talk about the studies that used conventional radiofrequency first, then cooled radiofrequency, and then cryoneurolysis. So, you have five studies on the use of conventional radiofrequency ablation at the knee. They are... none of them performed in the U.S. They ranged in sample size from 24 to 60 patients, and they ranged in duration from 12 weeks to 12 months. The most common comparator across two studies was intraarticular corticosteroids. One study used hyaluronic acid. One study used oral medications and physical therapy, and one used a sham procedure. So, quite a range of comparators.

The mean ages of patients involved in these trials is 53 to 69. They were predominantly female, as befits the condition. Three of the randomized trials did report BMI and in several it was high. Four of the RCT's reported mean symptom duration. The Ray study did not. The mean symptom duration ranged from seven months to seven years, quite a wide range. Two of them reported radiologic osteoarthritis grades. Those were the

Choi and El Hakeim trials, and in those grades, really moderate through quite severe osteoarthritis across those studies, and onto the results.

First of all, there were a couple of studies showing El Hakeim who reported a change in the Oxford Knee Score from the baseline level. There was a statistically significant benefit in the radiofrequency group compared to the control group at months one and three, but not when that was in the Choi study, and the El Hakeim study that was found, as well, but not at months six and 12. The WOMAC total was reported across most of these studies, not all. At week 12, in the Ray study, there was statistically significant difference. At that same time period in the Sari study, not a statistically significant difference. In the El Hakeim study at six months, there was a statistically significant difference in favor of the intervention group. Four studies measured pain using the VAS at three months. They all showed a statistically significant lower score in the treatment group with radiofrequency, essentially all of the studies, except for the Qudsi-Sinclair study. Patient satisfaction was reported in a couple of studies and was reported as being greater in the radiofrequency group compared to the control group at both months one and six.

So, in terms of the grade findings across these studies, what I will say on the grade tables, we needed to pick outcome measures that were common across studies at time periods that were common for these outcomes, and so for function in this group of studies, we took either the WOMAC total score or the Oxford knee scale at three months. That was the longest time period where there was a common outcome to pool across these studies. At that time period for that kind of finding for function, four randomized trials did find statistically significant and probably clinically meaningful improvements with radiofrequency ablation, one of those studies found no statistically significant difference between the groups. Overall, the quality of evidence is very low. We downgraded it two levels for serious risk of bias, one level for indirectness. On the pain outcome measured with either the VAS or the NRS at three months, three randomized trials found statistically significant and likely clinically meaningful improvements favoring radiofrequency ablation. One did not find a significant difference. Again, very low quality of evidence, and similarly downgraded for serious risk of bias and indirectness.

Now, let's turn to the one randomized trial on cooled radiofrequency. This was done in the U.S. The study's primary author's name is Davis. It was done among 151 subjects and had a duration of follow-up of six months. The comparator was one of three intraarticular steroids. The choice was left to the center that was involved in the study. It was a multicenter trial. The mean age of the participants was 64, two-thirds of them female,

predominantly white but with some mix of population. The average BMI, the mean BMI is in the obese range, and the duration of knee pain, 115 months; 35% had fairly mild osteoarthritis using radiologic rating, 44% moderate, and 21% severe changes.

Mika Sinanan: Are these multiple injections of the...

Valerie King: No. It was a single?

Mika Sinanan: ...or a single?

Valerie King: Single injection.

Mika Sinanan: Okay.

Valerie King: It's important, and what you need to know about that is that we don't expect intraarticular steroids to last forever. So, that may be two, three, four months maybe.

So, looking at the outcome measures, the study reported using the Oxford Knee Score. There really was not a significant difference in these randomized groups at baseline, as you can see there. At months one, three, and six, there was a statistically significant difference in favor of the cooled radiofrequency group. At months three and six, this probably met the MCID level that we pre-specified. Then, they also reported a change in difference in group means from the numeric rating scale from the baseline. This is for the pain outcome. At months one, three, and six there does appear to be a statistically significant difference there, and it is likely to be clinically important at months three and six, but not so much difference at month one, even though it's statistically significant. It's not on the slide, but I will say that they did examine use of pain medications, as well. At baseline, about 25% of the cooled radiofrequency group were using pain medications, and about 35% of the intraarticular steroids. They did statistically test that and found that the proportions were not different, but I would caution you with that sample size to not simply rely on statistical testing but also to know that there was about a 10% difference in pain medication use. What they reported was mean opioid drug used at each time was not different between the groups, and that mean changes in the dose used were not different between either of the intervention group or the control group at each follow-up point.

In terms of grade rating, this study individually we rated as having a moderate risk of bias on the basis of the one study that did find statistically and clinically meaningful improvements favoring cooled radiofrequency at

the three-month interval. The quality of evidence we graded as very low. We took off one level for moderate risk of bias, one level for imprecision, that's because it is a single study. One level for indirectness, which is lack of longer term outcomes and the comparator intervention. For the pain outcome using the NRS scale at three months, all [inaudible] statistically and clinically significant improvements and very low quality of evidence for all the same reasons.

Finally, this is the last trial of the knee area, Radnovich. This is 180 people with a follow-up of 120 days, and the comparator is a sham procedure. Pretty similar mean age of 61, two-thirds female again, 89% Caucasian in this, and a pretty similar BMI of 29. Fairly longstanding OA pain, 73 months, and what you see in this study is a higher number of people at lower levels of osteoarthritis graded radiologically, so 52% were grade 2 in here, and 48% grade 3.

This intervention is cryoneurolysis to the infrapatellar branch of the saphenous nerve, so a little bit different targeting than what you saw in the other randomized trials of the knee. Using the WOMAC function subscale compared to baseline, and this is a... these squares mean different statistic. It was reported at the 30, 60, 90, and 120. It is statistically significant at every interval, except the 120 day interval, and probably for all of those interventions, close to meeting or meeting the MCID we had prespecified. The mean change in using the WOMAC pain subscale from the baseline similarly at all those points and similarly statistically significant, except at day 120 and again probably clinically significant based on the MCID. This study did also report quality of life using the SF-36 instrument and did not find significant differences between the groups.

Gregory Brown: Least squares change. I've never seen that before.

Valerie King: So, they look at the difference, and it's a difference compared to the baseline for each group. Then, they compare the groups. So, it really controls for what the baseline score was in that particular group. Does that make any sense at all? So, it's not an absolute change. It's a change... it's looking at the baseline for each group. So, for the intervention group, it's comparing the time interval against the baseline for that group. In the comparator group, the sham surgery group or intervention group, again, looking at the time interval compared to baseline and then comparing those two.

On the grade table, again, this is a single study. It was at high risk of bias. So, we downgraded two levels for serious risk of bias, one for imprecision

because it's a single study, and then one for indirectness for some of the similar reasons as the prior study. Using the function WOMAC scale and the WOMAC pain subscale for both of those, this trial did find those statistically and clinically meaningful improvements with cryoablation at that three-month interval.

Let's go to the shoulder. Three out of four of these studies were done in Turkey and one in Canada. The longest of them followed patients for six months. The other two for twelve weeks. They all had different comparators. So, the first study, Eyigor, 50 patients, looked at a corticosteroid injection at the glenohumeral joint and the AC joint and the subacromial space. So, there's three places, each got an injection. Gofeld, the Canadian study, only 22 patients in it, used a sham procedure. Korkmaz used TENS. Then Okmen used photobiomodulation therapy, which we would commonly know a laser, and that followed patients for six months, as well.

The mean age across these studies is 52-69 years, more than half and up to three-quarters were women. Again, that fits with the general age and sex breakdown of this condition. Three of these RCT's reported mean symptom duration, all but the Okmen study, and that ranged from 10 months to 34 months. Two of the RCT's reported what the underlying pathology of the shoulder pain was, and for about half the patients it was supraspinatus tendinopathy and for about the other half, it was a partial tear of that tendon. Then, there was a minority who had acromioclavicular arthritis.

So, looking at these studies and the SPADI total score, again that's reporting function at month three, the treatment versus the control group. Basically, three out of four of these studies did not find a statistically significant difference. The one that did, the top bullet point by Eyigor actually finds a difference in favor of the intraarticular steroid group, so the opposite direction from the intervention. Similarly, VAS pain, and this was reported as pain at night, it was statistically better in the steroid group, intraarticular steroid group at week 12 compared to the intervention group. No other VAS measures, and they measured a bunch of them, including night pain, rest pain, movement pain, and overall pain, were significantly different between groups. It was only that one measure of night pain in the Eyigor study in favor of the steroid group.

One of these studies also reported quality of life using the SF-36 and the Beck Depression Inventory. There was no difference between groups. Gofeld reported patient satisfaction was statistically significantly higher in the treatment group at months one and three but not at six months of

follow-up, and again, Gofeld, that was the Canadian study that used a sham comparator.

For the grade table, in terms of function, one RCT had a statistically and meaningful difference in favor of the intraarticular steroids, but that probably did not meet the MCID. The VAS pain scale was better statistically in the intraarticular steroid group, as well. This group of studies for these outcomes were rated as very low quality of evidence, and they were downgraded two levels for serious risk of bias and one level of inconsistency and one level for indirectness.

So, there were two studies that were procedures done usually for plantar fasciitis, and these were procedures that were done location under the medial ankle. The first study was Landsman. This used conventional RFA but only studied 17 patients and only across four weeks. This was a group of people who had pretty severe plantar fasciitis pain, and it was compared to a sham procedure. They did not report any functional outcomes. They did report change in the VAS pain scale from baseline to week four, and recorded the average pain and peak pain were statistically improved in the intervention group and those probably met MCID levels, as well. Because we were looking for function and pain measures to record on the grade table that were at three months, you'll see a pretty blank grade table for conventional RFA for plantar fasciitis based on this one study. The second study was done by Wu in Taiwan. This is also small and a short duration, 36 patients over 12 weeks, and a little bit less, but again, fairly moderate types of plantar fasciitis pain. Just to remind you, the baseline AOFAS score, this is ankle-hindfoot score, was 58, and this was the scale where 0 to 100 was the scale, and higher numbers indicate better function. So, these people were about 40 points off their perfect rating.

The change in that score from baseline was statistically significant at all timepoints from one week to 12 weeks. They are also meeting an MCID for that particular scale. This study did report pain using the VAS scale, as well, and similarly, these are statistically significant and meet the MCID for that particular scale.

So, for pulsed radiofrequency for plantar fasciitis pain, there were, again, very low quality of evidence for both the function outcome and the pain outcome at three months. We downgraded one level for moderate risk of bias, one level for imprecision, and one level for indirectness for both of these types of outcomes.

So, there are some common limitations in this evidence base. Those include fairly small sample sizes, an inadequate description of allocation

concealment in most studies, use of either suboptimal or inappropriate comparators, inadequate length of follow-up to assess the durability of benefit or the development of harm, fairly large or differential losses to follow-up in many of these studies. Then, across some studies, there were some additional limitations. Statistically, many of these studies, because they did have fairly high losses to follow-up used a last observation carry it forward technique when data were missing, which would tend to skew the results in which way it would go. It depends on the time period and level at that point. There was a lack of control when baseline predictor values were different between the intervention and control groups. In those cases, they did some modeling but often didn't control for important confounders like, smoking, age, sex, and weight. You do see a substantial placebo effect in the control groups across many of these studies. Several of them were funded by device manufacturers or had authors with financial relationships with those manufacturers, and some other randomized trials did not report either the study funding or the author disclosures.

For safety, based on the findings from the 13 randomized trials, there is really very little evidence of serious harm. I will say that most of the studies did not have a particularly robust method for assessing those harms, but most of them that were reported were expected and procedure related, and that's things like bruising or procedural pain. There were eight additional non-randomized studies included for safety. They were all rated as having a high risk of bias, and they had limited harms reporting, as well, but pretty much the same and kind of related to expected procedural effects.

Mika Sinanan: So, none of those patients, by report, developed neuropathic pain afterwards?

Valerie King: No, but I would caution you that the lengths of follow-up were fairly short. Yeah.

So, looking at the federal bases of MAUDE and the FDA device recall database, a full report of this is in Appendix G of your report. MAUDE, there really are very few reports of serious adverse events. Burns were the most common, but again, very few. The FDA device recall database actually had some recalled, but none of them were related to serious adverse events. They were related to mistakes in packaging or devices that fell apart when the package was opened, or devices that were cracked or something else, but they were all errors that were found before the device, fortunately, was used on a patient.

In terms of subpopulation, there really were no RCT's that reported procedural outcomes stratified by age, sex, race, or other demographic factors. One of these studies that I talked about earlier, Qudsi-Sinclair, was actually conducted in a very distinct clinical subpopulation so a small study with only 28 people, 14 in each group, and these were folks who had at least six months of persistent pain after a knee replacement, and they compared to an injection of triamcinolone into the joint, which is sort of interesting in a non-native knee. This is an example of a comparator that is probably an appropriate one, and I would say that the authors also say that in their report. You do see for the OKS function outcomes a statistically significant improvement in the conventional RFA group at one and three months, but not at six and twelve, and using the Knee Society Score function outcomes, there is a statistically significant improvement in the conventional RFA group at three months at one, three, and six months, but that is probably not meeting an MCID level, except at the three-month interval.

Gregory Brown: I'm curious, so they used Oxford Knee Score and KSS?

Valerie King: Yeah. They did.

Gregory Brown: So, they just picked whatever one?

Valerie King: Yeah.

Gregory Brown: Did they prospectively say which one they were going to use, or did they just [crosstalk].

Valerie King: In their methods, they say they're going to use both, and then they report both.

Gregory Brown: Okay.

Valerie King: But there's no trial protocol registered. So, who knows?

Gregory Brown: Okay.

Valerie King: No economic outcomes. I was really shocked by this actually, but there are some studies coming that we found in the trials registry that probably will report on this.

So at ClinicalTrials.gov, there are 12 ongoing and registered randomized trials that are expected to be completed between the end of last year and a couple of years from now. So, there are several on knee osteoarthritis

and it does involve conventional radiofrequency, pulsed radiofrequency, cooled radiofrequency, and MR-guided functional ultrasound. For foot pain, nothing that we reported in terms of interventions in the current review, but one trial using cryoablation for hip pain, osteoarthritis pain, there is one using cooled radiofrequency and a cryo-analgesia intervention for phantom limb pain. There were no trials registered in either shoulder or plantar fasciitis pain.

We included any guideline that discussed management of limb pain, whether or not that guideline specifically mentioned peripheral nerve ablation. Three of them did. Five of them did not. None of the eight recommended it. These are the five guidelines with no mention of peripheral nerve ablation. I understand that the American Academy of Orthopedic Surgeons for the mean guideline is under revision currently, and that it will include peripheral nerve ablation, as an intervention of interest.

For the three that mention peripheral nerve ablation, there is one from the occupational NED group that is of poor methodologic quality and quite old that said that there is no recommendation for or against the use of diathermy for the treatment of basically tennis elbow. The American College of Foot and Ankle Surgeons has a fairly recent guideline looking at acquired infracalcaneal heel pain, poor quality, and it says that the evidence on bipolar radiofrequency treatment for chronic refractory plantar fasciitis is uncertain. So, they don't make a recommendation one way or the other. Then, the Association of Extremity Nerve Surgeons, also a poor quality guideline, does not actively recommend nerve ablation for the treatment of Morton's Neuroma.

Gregory Brown: Has anybody even ever heard of that last group?

Valerie King: They were in the guidelines database. That's all I know. For payer policies, there's no new Medicare National Coverage Determination related here. The local applicable coverage determination that is applicable in Washington by Noridian is a little bit vague but says that thermal, not pulsed radiofrequency, is covered for a variety of pain diagnoses, including knee, hip, and shoulder pain. What is vague or confusing is the title of the LCD is on nerve blockades rather on nerve ablation, but I think that we interpret this as the Medicare LCD probably does cover these procedures. It's just, I would say I'm not 100% on that. For private payers, AETNA, Cigna, Regence do not cover, and it gets quite detailed. So, AETNA does not cover for pulsed RF for any indication, cryotherapy or patellar denervation for knees. Cigna does not cover peripheral nerve ablation, including cryoablation, radiofrequency ablation, or any other kind of

ablation, and they do not cover radiofrequency lesioning for pain resulting from plantar fasciitis. Regence does not cover nerve ablation, including cryoablation of the upper or lower extremity peripheral nerves, nerve plexus, or other truncal nerves. Ablation using magnetic resonance-guided focused ultrasound and high-intensity focused ultrasound procedures for pain is similarly not covered.

In summary, there is very low quality of evidence that does favor peripheral nerve ablation to improve some short-term functional and pain measures in studies of knee pain, shoulder pain, and plantar fasciitis pain. All studies have some significant to very significant methodologic limitations. Seven of the 13 reported some improvements in short-term function and pain measures that were both clinically and statistically significant. The improvements tend to be fairly small in magnitude and not always consistent across studies. The positive outcomes are only reported sometimes in one trial, one scale, one subscale or one time period, and the evidence, even though we concentrated on outcomes at three months, is pretty limited to those that occurred within three to six months.

There are no studies that offer head-to-head comparisons with these techniques, and we found no randomized trials for treating pain at additional anatomic locations and I know the medical directors were quite interested in hip, but none of those. The potential harms are probably pretty minimal, but I will caution you that they are quite poorly reported. We know that harms and adverse events are under-reported in registry databases like MAUDE or the FDA recall database. No studies reported anything on economic outcomes, but maybe there's help on the horizon that there are some ongoing trials.

No clinical practice guideline that we identified makes a recommendation to use peripheral nerve ablation for limb pain. Medicare at the national level and three private payers in your region do not cover it. It's probably covered as conventional RFA in your local Medicare coverage decision, and really there is a paucity of evidence to support procedures, and that really gets reflected in the payer recommendations, but also probably the guidelines. I've marked up an evidence map if you want me to give it to you in interpretive dance, but I don't have a slide of it.

Gregory Brown: It seems like you are grading everything on an absolute scale, and I'm trying to understand the relative scale. So, virtually everything got downgraded three or four levels if I was following correctly. One of them was for indirectness and the comparator.

Valerie King: So, indirectness can be for a whole lot of reasons.

Gregory Brown: Okay. But...

Valerie King: So...

Gregory Brown: ...at some time, you said the comparator, so.

Valerie King: ...so, sometimes it was the comparator. So, indirectness is that the study does not exactly meet your PICO.

Gregory Brown: Okay.

Valerie King: So, you have indirectness in the population, the intervention itself, how it is performed, the comparator that's used compared to what you might have seen or thought was optimal, and then certainly, it's the outcome measure, one that is meaningful. So, indirectness happens in all those areas. Indirectness can also creep in because the study was done in a country that is not like you. So, the studies, for example, that were done in Canada, I wouldn't downgrade for indirectness. Those that are done in Turkey, I would.

Gregory Brown: Okay. So, for comparators, what does the evidence support for comparators for the knee osteoarthritis subgroup?

Valerie King Yeah. So, a little bit depends on the outcome and the timing interval that you're looking at. So, I think the clearest example of a really inappropriate comparator is in the Qudsi-Sinclair study that looked at people who were post knee replacement. So, using steroids in the knee joint of people who don't have a native joint is probably not really doing much. It's essentially a sham.

Gregory Brown: I agree completely, but that's the one. So, the other studies that looked at knee arthritis, they looked at diclofenac, an NSAID. They looked at paracetamol or acetaminophen for us. They looked at corticosteroid injections. So, what's the evidence supporting those treatments?

Valerie King: You know as well as I do that pain medications, be they acetaminophen or a non-steroidal or an opioid, and can have some effect on knee osteoarthritis pain. These patients were often selected as people who had failed those kinds of conservative interventions. In many of the studies, and I didn't about this, patients were actually prohibited in the comparator group from taking those medications or were...

Gregory Brown: Prohibited... I don't...

Valerie King: ...or were not allowed to increase or change their doses or their medications. There were people who were enrolled in some studies who had been taking an NSAID and then were not allowed to take it going forward and were only allowed to take Tylenol. So...

Gregory Brown: Okay.

Valerie King: ...there were issues like that about the comparator.

Gregory Brown: Okay. So, I... but I guess what I'm trying to understand is, there's a recent JAMA article looking at the effectiveness for NSAID's for knee arthritis. Their conclusion is that there is no data at 12 months. Then, there's a JAMA article looking at NSAID's, which you've had for years, and everybody would tell you is your first line of treatment for knee arthritis, but apparently, there's no evidence for it. So, I guess what I'm trying to understand is, there's no evidence for NSAID's, but that's what we all do. There's no evidence for this, so how do I compare, other than the studies that you have.

Valerie King: Yeah. We are internally looking at this group of studies, and I will say that some of them used comparators or used comparators in ways that were methodologically problematic. That's why they got downgraded.

Gregory Brown: Alright. Fair enough.

Sheila Rege: Any other questions?

Austin McMillin: I was going to ask, like, what would be an appropriate comparator, because these are patients who typically have had difficult ongoing pain, had multiple... tried multiple things. Is sham not considered to be a valuable comparator for a procedure?

Valerie King: Yeah. I think if you're trying to look at the internal validity of a procedure, as long as the groups are treated equally aside from the sham. So, if both groups are allowed to take oral medications or both groups are allowed to have PT, then a sham is, for internal validity, quite a good way. It helps limit the placebo effect.

Austin McMillin: I'd also comment to [inaudible] what the medications available to people are in this study were.

Valerie King: What I get concerned about is when it is differential.

Austin McMillin: I also was looking through Cochrane reviews about the duration of effect for things and evidence, and I don't see many things with any evidence beyond six months.

Valerie King: Yep.

Austin McMillin: So, when we're looking at the duration of treatment, did they follow... what would be ideal on your... when you think about that?

Valerie King: I think probably the clearest example is something that gives me pause and caution is the... we know that the use of repeated injections of corticosteroids at the knee over time will accelerate the osteoarthritic changes in the knee and actually make things worse at a certain point. So, for people who are going to have their knee replaced and just need to get around for a vacation that they've got planned, that may be a really, really great intervention. For other people, maybe not. I think it's a cautionary tale with steroids. So, there were some people in review articles around these techniques who said it's one thing if you're using them for folks who are bed-bound and in intractable pain and not weightbearing, and it may be quite another if you ablate the nerves at the knee of somebody who is active and then is going to go out on their already compromised knee and be more active on it and accelerate changes. So, I don't have trial evidence that states that, because the durations are so short, but it took a while for injectable corticosteroids at the knee to show evidence of harm, too. So, it's just... in the back of my head, [inaudible]. I think about is there some harm that isn't apparent, including joint degradation that we just simply cannot see at these types of time intervals. It's just an open question.

Gregory Brown: I don't think it's an open question, because there isn't any knee that I can't do a knee replacement on. You can't degenerate your knee to the point where we can't do a knee replacement. So, that argument has no validity. I agree with you about the corticosteroid. The other thing about the corticosteroid, though, actually is the evidence and large databases reviewed that corticosteroid within six months to a year prior to a joint replacement can increase your risk of infection 50%. I need an injection for my knee for the summer so I can get it replaced in the fall, absolutely the wrong thing to do. So, anyway, I think there's some side effects... others that we can discuss later, but yeah, anyway.

Sheila Rege: Any other questions?

Seth Schwartz: I have a question. I'm not quite sure if it's for you or if it's for Dr. Stacey, but I'm just thinking about this in terms of what actually happens with these patients. So, what we're seeing is, you have these two interventions

and these trials. The RF group does slightly better over a three to six month window. Then, they kind of migrate back together again. So, I'm curious are we seeing regression of the mean, or are we seeing improvement overall. What's happening in these groups? So, the differences are becoming less, but what's happening to the overall group over this year timeframe that we're looking at. Maybe you know what happens to their overall scores, as someone who cares for these people. I'm curious what your thoughts are there.

Brett Stacey: So, there are Kaplan-Meier survival curves for lots of RF procedures that show that somewhere after six to nine months there starts to be a fall-off and continued success... measures being success, whatever that was, 50% reduction of pain, 30% reduction of pain, whatever it is. Then, there tends to be a group for whom the tail goes on forever where they seem to have a prolonged effect. So, I think what happens is, sometime after the six to nine month range of time, the group that are going to have, when the nerves regenerate, the pain starts to come back, or their disease advances, or something else happens, and it kind of falls up. Then there's the other group that that was enough to put them over the edge, and they did well for responders. So, I don't really know the answer to that. I think there's just not a ton of data even being collected. There's not a ton of data being collected beyond the six-month period of time to have an idea.

Valerie King: Just for the background for this, I looked for studies that just gave prognosis of these procedures running out in time, and there's... it's certainly a concern across a few of them related to pain returning, because nerves do grow back when they're sensory nerves, and the pain returns, or the disease process gets worse, but there's really not a lot of data. This was mostly expert opinion, and it's really poorly studied.

Seth Schwartz: Okay. And then my follow-up question is, pain is a difficult thing, and how you judge duration. So, six months of pain could be absolutely awful. So, is it meaningful to say that six months of pain relief from a procedure is a meaningful change, even if we watch over time that the pain effect goes away? So, I'm struggling to have a framework for this in terms of how valuable is a six-month improvement in pain for patients in this situation and again, Dr. Stacey, if you have some thoughts about that.

Brett Stacey: I was thinking about botulinum toxin injected every three months for migraine prophylaxis. That's pretty frequent recurrence to denervate something, and this is less frequent than that. So, six months seems like a good response, but I think we don't know what the response is, because the studies... several show six-month effect. There's not many looking at 12. So, it's often more than six. Who knows?

Sheila Rege: And we are about ten minutes over. So, do we have another question?

Mika Sinanan: Just briefly, it appears to me from your analysis that the benefits seem to vary by the device, pulse versus regular versus cooled versus cryo. Right? So, would it be reasonable to say that decisions we make or recommendations we make based on the evidence are not necessarily generalizable to RF treatment? That it really comes down to the technique that's used?

Valerie King: I think that's true at the knee. Yeah.

Mika Sinanan: And the same... and it's not generalizable across all sites, as you point out, because there seems to be a lot of variability about the benefit depending on where you look.

Valerie King: Yeah. So, shoulders are really different than feet are different from knees. So, the anatomic site makes a difference, and it plus/minus the ablation technique may also present differences. So, we can only say what is included in the studies that were eligible for this. We only... the knee was the only anatomic area where we saw three different techniques being used, but our search was broad. We were willing to take ablation done by cold knife or chemical or anything, but we only found those three techniques.

Sheila Rege: Anybody for a last question for this side, or? Okay. Well, thank you very much. It's 2:22. Shall we break until 2:30? Will that give us enough time? Okay.

Anybody want to start?

Tony Yen: I could start. I have a question for our expert, our clinical expert. I'm just trying to understand this a little bit better, in terms of how this really works in terms of the actual procedure. It seems like this is fluoroscopically-guided. Am I correct?

Brett Stacey: Yes. There are descriptions of doing it under ultrasound guidance, as well.

Tony Yen: Okay, but the current standard is that either ultrasound guidance or fluoroscopic guidance?

Brett Stacey: Probably fluoroscopic, but I think both would be acceptable.

Tony Yen: Okay.

Brett Stacey: Fluoroscopic is way more standard.

Tony Yen: I'm just trying to understand how fluoroscopic guidance ... help me understand how this can get anywhere close to the nerve. I'm assuming that the nerve is in a specific area that you will... I just don't understand the procedure.

Brett Stacey: Actually, I love the picture that was shown of the nerves that you had shown, because it... there's a little place in the bone where the nerve runs. So, all the dissection is supposed to be relatively clearly associated with specific parts of the bone at the three main landmarks, which are very visible on fluoroscopic. See, you do not see the nerve. In fact, most fluoroscopically guided... all fluoroscopically guided procedures, you never see the nerve. You see the bony targets where the nerves are associated. So, the thing to know about the knee when you're doing fluoroscopic procedures, which people who operate on the knee will know this, it's very important to have a true AP or true lateral view. It's very important to have that so you really know where you are. These nerves come in a... they kind of loop around towards the joint, and they start to branch off, and that's why a larger or longer lesion is helpful. So, if in person A it's a little higher up, a little more anterior, a little more posterior. You've covered the area where they are. So, the targets... the bony targets are selected to be relatively far away from tendon insertions or from major vessels and close to where the nerve runs.

Tony Yen: So, the probability of actually ablating the nerve, is it good or is it kind 90% or 80%? What do you think?

Brett Stacey: I don't know what the number is. It is good, and when I personally do this, I am an "I don't want to miss it" kind of person. So, I do multiple lesions at each location. So, I do more shots. I go more anterior, more posterior. I do repeated innervation, I mean, denervations, and the different techniques use different size cannula or different types of cannula that make different size lesions. So, the cool techniques make a larger lesion. The radiofrequency probes come in different gauges and different lengths of that with tips. I would tend to pick out a larger probe with a larger tip to make a larger lesion and then typically make more than one lesion to not miss things.

John Bramhall: I don't mean to be venal in any way, but when people come to you specifically for this therapy, they have to pay for it? It seems like it's not covered by...

Brett Stacey: Well, it's covered by Medicare.

John Bramhall: It is covered by Medicare?

Brett Stacey: Yes. It is.

John Bramhall: Oh, okay. Alright. Sorry.

Brett Stacey: And it is covered by some of the other insurance policies. We haven't had anybody pay for it out of pocket in our clinic.

John Bramhall: Alright. So, most of the people coming, it's a covered benefit for them.

Brett Stacey: Yes.

John Bramhall: Again, I wasn't being venal. It's just that...

Brett Stacey: No. It's okay. So, most [inaudible] aren't for the technique, though. They're for, like, persistent knee pain. So, they typically leave me to more conservative care first. Then, the way that I do it, which was not consistent across these studies, was I do a diagnostic block first. The patient must have an adequate response to diagnostic block before I go forward with doing a destructive technique.

Mika Sinanan: Do you have a comment about the different techniques, cryo, pulse, standard, and cooled?

Brett Stacey: Yes. I think pulsed radiofrequency ablation is a misnomer. It's pulsed something to the nerves. It's applying energy in the area. It's not particularly a [inaudible] technique. There are very, very few studies that show anything with a longterm result from pulsed technique. So, I think pulse is in a different category, and I'd be totally happy if you had a wholly completely different ruling for that. Cooled RF and traditional RF are similar neurodestructive techniques with the same target tissue temperature of 80 degrees centigrade or above, the main difference being the shape of the lesion is more circular with the cooled, and the size of the lesion is larger, so you're less likely to miss something. The other thing with the cooled technique is with the traditional RF, something elliptical, like a football-shaped, and the angulation at which you put the probe in matters. With the cooled, it's more round, so the angulation at which you probe the tissues is different. So, the patient I mentioned to you that had previous instrumentation from metastatic cancer disease, I could go around the metal at a different angle and not have a problem making the right lesion. So, cooled has some advantages and the angulation doesn't

matter if there are anatomic considerations. Cryo is probably less destructive, more cumbersome equipment, less well studied. The one study targeted unusual single... didn't have the same kind of target so I don't know how you would evaluate it very well.

Mika Sinanan: In clinical situations where these techniques are used, would you have a range of options, or would you routinely choose to use cooled or cryo as a kind of a single technique?

Brett Stacey: With the topics being discussed her, which are the limbs, I would tend to use cooled. If the equipment wasn't available, I would use traditional RF and probably do more lesions.

Mika Sinanan: And would you choose traditional having both available?

Brett Stacey: I would pick cooled.

Mika Sinanan: You'd always pick cooled?

Brett Stacey: It takes longer. It's a little bit more effort, but it's okay. The lesions are bigger.

Sheila Rege: It seems like knee, shoulder, and plantar fasciitis, what's the distribution? I mean, do most people come in for knee pain for this procedure or shoulder?

Brett Stacey: In our clinic it's knee, knee, knee, knee, knee, and then maybe a little bit of hip, and I think that's about the whole list for us. I have done one pulsed RF for the suprascapular nerve, and I thought it was kind of like doing a sham procedure on a patient, since I realized the literature was not very good, and I didn't have the choices for what to do for this person. I thought I wasted my time and that person's insurance money. I like if there's good data there, so I don't do that. Essentially...

Kevin Walsh: Excuse me. Could I ask you to talk more directly into the microphone?

Brett Stacey: ...oh, sorry. So, for the pulsed RF for the shoulder, I've done it exactly once, and it didn't do anything, and I decided after that, after looking at the literature that was available not to try that again. Most of the time in our clinic we see people with knee issues end up with this and occasionally hip. One of my colleagues published a very elegant anatomical study looking at the innervation of the hip minimal to radiofrequency approaches. So, he does that a little bit more than I do. So, it's really knee and hip for us.

Sheila Rege: So, in terms of continuing with the discussion, should we just... I'd like to go around the table getting thoughts on how people viewed the data and just thoughts. This time, we'll start on this side.

Austin McMillin: May I ask another question before we start the discussion?

Sheila Rege: Absolutely.

Austin McMillin: I heard you use the word no longterm results for the pulsed, what is longterm?

Brett Stacey: I really have not seen much reported beyond three months with a positive outcome for any target.

Austin McMillin: So, what's your view of the studies and evidence that we were presented with? Really, looking at only three, six, and twelve months periods, really nothing further than that. Are you aware of information that hasn't been presented that follows patients for longer showing more longterm results or outcome?

Brett Stacey: No. I'm not aware of anything. I think that there are very few studies of any intervention whatsoever for the knee that doesn't involve a surgical intervention around six months. Then beyond 12 months is extremely uncommon.

Austin McMillin: Then, one last question is, for the patients that you're seeing, the vast majority of which are knee patients, we saw that in the evidence that was presented, I noticed that many of those patients had high BMI, obviously weight and conditioning is a factor for these patients. How many of the patients that you are using this procedure on are actually very close to knee replacement anyway?

Brett Stacey: I don't know if I can give you a good estimate of that. So, the populations... there are different patient populations. There are people who want to put off the knee replacement. They're young or they are afraid of a knee replacement, or they had a relative with a bad outcome or something. There are people who have already had the knee replacement and had persistent pain. Patients who are medically compromised and not appropriate necessarily for the rehabilitation after the knee replacement, so they want to put it off. So, there are different groups of patients that really feel quite different from each other. Then, I do things maybe a little bit different than everybody else, but I tell people two weeks after the procedure, it's a good time to now go and revisit the physical therapist and

go back and take full advantage of this and get yourself in the best condition you can.

Austin McMillin: Maybe one last question in that regard. Given that sensory nerves, including around the knee, contribute to proprioceptive function, if we're ablating the nerve and potentially compromising the rehab on the back side, how do you view that? Or how do you... do you think it's a complication to rehab on the back side once you've cut the pain out of the picture or reduced it or mitigated it somehow?

Brett Stacey: So, this is kind of back to Dr. Franklin's comment when he talked about denervation being complicated. This is not anesthetized any. So, there is still sensation coming from it. You can hit it. You can tape it. People are very aware of it. It seems to decrease the input from the knee, and these appear to be nerves that, for patients who are more sensitive to what's going on in their knee appear to be more important once we're conducting that, but I have not seen nor heard people discuss people losing proprioception and that kind of thing. There are reports of difficulties, with radiofrequency, at the upper cervical spine, for instance, which is quite a bit different, and with the targets being denervated, being uniquely and totally innervated by the nerve you're targeting. So, unlike the knee where this is shared denervation for multiple [crosstalk].

Austin McMillin: [crosstalk] motor function is fine, too.

Brett Stacey: But [inaudible] deeper sensory nerves.

Janna Friedly: You had mentioned that you can do a knee replacement on anyone. So, if this is a treatment that works for three months, six months, something like that and they have to get repeat, if it's a chronic condition. It's not going away. This is a degenerative condition, and that means that you would likely have to do repeated procedures every six months or so for pain relief. Is there any data or concern about repeated procedures and any sort of longterm complications?

Brett Stacey: I would have to say that's a misconception and a difference of opinion... understanding of this. So, let's back up with that. So, I A, don't know how long they lost. Most of these studies stop at six months. We don't know how long the effect is, number one. Number two, if someone is now able to rehab their knee, the structure of their knee is not what's determining whether they have pain or not. Right? We know, for instance, in the lumbar spine, you're very well familiar with this, that what the spine x-ray or MRI looks like doesn't determine how much pain someone has. So, they're able to rehab their knee, and they don't have further progression

of the disease, they may not need a repeat. I have seen someone in clinic recently who I did this on two and a half years ago, came back to see me for his back pain. The knee is not an issue still. So, the response is quite variable. I have not repeated it. I know some people do repeat it. So, I think that we don't know that. I think it's a separately different issue to tell you the truth about whether you repeat and what period of time that should be, if there is repeating what the long term effects are, if you relieve someone's pain for a period of time and then they are able to change their body habitus or their exercise routine or something. Then, they don't need it. So, I don't know that.

Janna Friedly: I think the question is, if you were to think about coverage this procedure for those conditions, are there limits on the number that you could do in a year or are there concerns with repeated procedures where you're denervating the nerves repeatedly.

Brett Stacey: I think there would be concerns, and I think it would be a great topic for discussion for a panel. We just talked about that. I mean, I don't think it should be you repeat as often as you want forever. So...

Janna Friedly: Well, that's why I was asking. That data [crosstalk].

Gregory Brown: I think a better way to say it is, if we're making evidence based decisions, you just said there's no evidence about repeat nerve ablations. So, that [crosstalk]. We can't make a decision, because there's no evidence on which to make a decision.

Mika Sinanan: A question before I make my comments, actually to Greg. Do you see this as a strategy, and it kind of falls from both the previous questions, that avoids or significantly delays the knee for a knee replacement? How do we think about that?

Gregory Brown: So, can I ask to give my discussion before you, and I may answer it all in that process. Again, it's... so a little background. I was co-chair of the American Academy of Orthopedic Surgeons clinical practice guidelines on osteoarthritis of the knee in 2013. Since then, we published a meta-analysis on hyaluronic acid because it is a very expensive placebo. It is nothing more. Last May, we published a network meta-analysis on non-operative treatments. The number one most effective treatment for knee arthritis, one randomized clinical trial in the New England Journal of Medicine, is a knee replacement. Without a doubt, it is the best treatment for knee arthritis. Now, that doesn't mean that's your first treatment, but when you have endstage arthritis, that is the singular best treatment for knee arthritis. So, short of that, the network meta-analysis says the

number one treatment, most effective treatment, short-term four to six weeks, because that's the only timeframe we could find enough RCT's to compare across this network, naproxen for pain and function. For function alone, naproxen. For pain alone, corticosteroid injections. The problem is, we all know the problem with NSAIDs and contraindications for GI problems, renal problems, people on a chronic anticoagulation that it interacts with. So, there are so many patients with hypertension, diabetes, and these other issues that can't take them. Corticosteroids absolutely can progress arthritis, and the increased risk of infection around the time of joint replacement, if it's within six to twelve months is horrible. So, the biggest problem we've had lately is, insurance companies saying, well, you have to have an injection before you can have surgery. That's the last thing you want to do before you do a knee replacement or a hip replacement on somebody. So, the issue is, what do we do for people that can't have an NSAID or can't have a corticosteroid, aren't quite ready for surgery, or it's contraindicated, or in this state, now that we have the BREE criteria. Your BMI is over 40. Your hemoglobin A1c is under 8. We need some other optimization. What are we going to do to manage your pain until we can get you to surgery? So, I think this is a great option. So, the paper we're writing, I agree with all the concerns about them, but every single paper, nerve ablation was better than the comparator. That was NSAIDs, corticosteroid injections, HA, whatever. So, to me, if I were making the rules, I would use this for grade 3 or 4 osteoarthritis where NSAIDs and corticosteroids are contraindicated, or surgery is contraindicated or being delayed. I would eliminate HA coverage, rereview that next year, and say we now have a treatment that is effective with no side effects and use it in that situation. That's where I would put it. Ms. Jackson, I don't think you're still here, but my mom was in the same category. She needed a knee replacement but she had been a diabetic for 50 years, type 1 with insulin. She had poorly controlled glucoses with the corticosteroid injection for some spine at one point. She certainly couldn't take NSAIDs. She was a high risk surgical candidate and if I would have had nerve ablation, I would have done it in a heartbeat and never would have let her get HA injection, but I think that's a perfect operation for someone whose got... I mean, especially if two and a half years later you have some people... I know it's anecdotal, but it's certainly better than HA. HA, the study published two years ago, won an award. Nonoperative treatment costs for knee arthritis two years prior to surgery, $20,000. Our bundle payment, we get $24,000 to do a knee replacement under CJR in this state; $20,000 for non-operative treatment, and 45% of it was for HA, $9000 over two years for ineffective treatment. So, the comment from industry that it saves money, I actually think it's true. I would do this any time before I'd inject HA. So, anyway. Sorry. That's why I dismissed myself as chair.

I'm just too passionate about this. I get carried away. Did that answer your question?

Mika Sinanan: Yes. Thank you.

Sheila Rege: So, we're not starting... just comment. We're not looking for... just comment on the evidence and go around the table. We'll start with Kevin there.

Kevin Walsh: I would take shoulder and foot out of the discussion. I don't think there's evidence to support either of those. I see some evidence suggesting benefit for the knee. I am troubled by the fact that the length of benefit that is demonstrated is, in my mind, microscopic compared to the duration of time that most people put up with knee arthritis. I don't know how helpful that is. This kind of hypothetical discussion around the person who can't get their A1c controlled to get their knee replacement, and wouldn't nerve ablation be great, is... I mean, I have a bus load of patients who fit that criteria, but that's not what this is about. This is a much more generic and open-ended discussion. The question of all of its possible applications is left off the table. I guess I go back to the duration of benefit, of demonstrated benefit and just think that it's inadequate to support.

Tony Yen: I think it's interesting that our vendor has, I think most of the evidence over here is classified as very low. The definition of very low is no confidence in the estimate of the effect or intervention. That's the evidence that we have right now. What is interesting is actually what our expert is saying, and Greg. I really appreciate your opinion, as well, in terms of what's actually done in practice and what you observe in practice, but at least what the evidence shows is that there is not much there. There may be something there, but there's not a whole lot that I can see right now.

Chris Hearne: I agree with Kevin that we should definitely, I think we can set aside shoulder and foot. I don't think there's much there at all. I'm torn on the knee evidence. I think that's the one we can discuss, but I think tabling the shoulder and foot would be my first thought.

Laurie Mischley: I would agree, the shoulder and the foot for me are clear that there is no evidence, but I am also torn about the knee evidence. There are a number of studies. They are all different. They are all very small. They all have flaws, but the effects are all consistent for the most part, in terms of the response, as you mentioned, regardless of the comparator, and there isn't a lot of longterm safety data on which to go by, but it doesn't appear to be a high risk procedure, as far as we can tell, that has ramifications longterm for these folks. So, I'm a little bit torn. I'm struggling a little bit with

understanding how to compare the risk of bias in these studies. Some of it, there were a lot of things that were sort of lumped together, in terms of location of this study. Well, how do I interpret a study that was done in Turkey versus here? I'm not quite sure how that weighs in my head, in terms of risk of bias compared to some of the other studies that we have looked at today. So, I'm struggling with that. I think that there are a number of trials that are coming out. So, I think in a few years, we're going to have a lot more data, and there's a lot more studies that are going on, and my gut feeling is that that will show that there is some benefit, but I'm not sure that we're there quite yet.

John Bramhall: Yeah. So, the presentation of the primary information was pretty heavy going for me. The [inaudible] of the WOMAC is a little hard. So, I relied heavily on the interpretation of the vendor to interpret the data for me in the sense that the presentation is that it's not strong data in support for the knee. I agree with the other regents, as well. I have a... philosophical is a big word, but I do think the... I feel uncomfortable about the idea of removing sensory input by ablation in order to increase the utility of a joint. It just seems to me that you've taken away a piece of information that the body normally uses to protect, and I wouldn't go too far down that pathway. It's just that removing the sensory flow, allowing the joint movement, isn't necessarily in the longterm beneficial it would seem to me. So, I see this... I do think... I am impressed by your testimony of your individual activities with patients. It gets them over a hump. It gets them to a new place. I sense that there is value here as a temporizing solution for some patients. I sense that. There's no data on the longterm outcomes, though. I can't comment on it. I think the data are weak, but when I say that, I'm relying largely on the vendor's interpretation of the data quality.

Sheila Rege: To follow up on that, on the safety issue, is that something in clinical practice, have you had issues with safety or with the ablation? What the vendor said was just burns, but have you seen anything more because of...

Brett Stacey: So, in terms of actually seeing, I haven't really seen anything significant. Patients have pain for up to two weeks after, because it is a neuro destructive procedure, and it takes a while to heal from burns inside you. I've not seen any of the grounding pad kind of burning.

Sheila Rege: On like an amputated limb, like the residual pain.

Brett Stacey: I haven't seen that. I tend to agree, honestly, with what you said, and what you both said about neuro-destructive things is what some people said. If you had an alternative, if you could inject something that would

regenerate the cartilage and open up that medial compartment, I would love that. I, myself, have bad osteoarthritis in my right knee, and I would love to have some kind of thing to make it better. So, I understand those concerns. And that was actually part of my hesitation when I first started doing this was I was a little skeptical about the innervation issues and about what was going to happen with that. I realized that we were kind of attacking the primary three nerves but leaving a lot of other innervation intact. It's a little... it's not a clear issue, I'll say, but then you have patients for whom there aren't really great options. I think it's a reasonable choice in that situation.

Chris Hearne: I didn't see any concerns with the cost data. I thought that was reasonable. I thought that it looked like things were under control. It was not out of the ballpark certainly when you're talking about $100 here or $500 there. The safety didn't seem to be a problem for me. I did have concerns about just the overall quality of the data, there are statements about bias. That didn't really get me. If I was to make a decision, because I've got an arthritic knee, as well, if I was to make a determination about what I was going to do about that based on the data, it would bring me, I wouldn't be able to make the decision based on the studies that were put forth today. It seems to me that I would be making the decision about the procedure based on a point of desperation, not data. I think that that's what's driving a lot of people in healthcare is that they've got their problem pushed so far down the line with weight and inactivity and sedentary lifestyle, etc. that I get a little bit concerned about the procedures and recognizing that six months of pain relief might be a life-changing experience for somebody, but the data leaves me a little concerned about this being the way now. I think it's encouraging that there is lots in the hopper, in terms of researches coming out, and I don't think we were presented with some of the research of the meta-analysis that you may have gone through to be able to factor that in and weight that. So, the data just leaves me a little bit short.

Seth Schwartz: It's a pleasure to be sitting on this panel of patients today. First of all, I totally agree with Kevin. I think there is really nothing there on shoulder and foot. I think that clearly the data for knee is weak. I think we do see a consistent trend towards a difference, but it's just significant in these weak trials, and I don't know quite how to interpret the duration of effect. I think... because I do think six months of pain could be pretty dramatic for somebody who is otherwise struggling. So, when I'm balancing that, it's a procedure that has fairly low risk and fairly low cost, and if you can get six months of pain relief, then that might... that could be pretty meaningful for patients. So, even though I think not being terribly desperate, but just thinking in terms of limited options for these patients, I think there is

probably a role for this procedure, and I think we could probably construct a situation where we're not simply offering it to everybody, but clearly if you've run through the other options for managing this condition, and there aren't other good options available to you, then I think that there's enough here to allow it to be an option for our patients at this point going forward.

Mika Sinanan: So, I agree with the previous comments about taking shoulder and foot out of the equation. It does seem to me that the analysis that downgraded the quality of the data for knee treatment, especially the cooled RF, the greater the quality at multiple levels, or of the analysis, the interpretation, in ways that are probably more extreme than we have seen for other similar types of data and probably ought to be applied to the comparative best available options for the reasons that Greg has said. They have acclaimed limitations. So, I agree with Seth that I think that there probably is a benefit to this. It needs to be carefully managed. The additional data that's coming out in the next few years may change that. The option of saying we're not going to cover something and wait for new data for something that is relatively inexpensive, and for which we have a body of, albeit moderate date, but trend is all positive that it is beneficial, at least for a period of time, would push me towards supporting it with qualifications or with conditions. What I don't know... I didn't see anything that suggests cryotherapy is of benefit, and I don't know whether we can put conditions that actually limit the types of RF reasonably or whether we're approving all RF.

Sheila Rege: Any more discussion?

Gregory Brown: I have a technical question and a comment.

Sheila Rege: Yeah.

Gregory Brown: Technical question, John, when you're taking the cosign of the Oxford Knee Score, is that in degrees or radius?

John Bramhall: Yes.

Gregory Brown: The second question is, the clinical practice guideline for 2015 on osteoarthritis of the knee clearly states that opioids are not effective for chronic knee pain. So, this is the other issue, and there was a comment made by industry, again I think appropriate, it is a non-opioid treatment for chronic knee pain.

John Bramhall: Can I ask... there are three or four different techniques for this ablation of the nerve, as the cryo, which is... is there an objective way of monitoring the sensory flow through the lesion after you've done any of the interventions, because it seems like if you destroy the sensory nerve in a location, it wouldn't matter what the modality was that you used to destroy it. That's all I'm...

Brett Stacey: So, it's not so much the surface innervation, though. So, the surface innervation is left relatively intact. So, it's difficult to quantify that.

John Bramhall: There's no electrophysiologic method for objectively saying transit through this nerve is gone?

Brett Stacey: No. So, describing the methods of some of the studies that were presented with stimulation before you lesion with a 2 Hz or 50 Hz stimulation for the patient to feel reproduction of their pain in the area. So, say you're stimulating the sensory nerve, and then you lesion. That's about it. There's nothing else. I know, as Janna knows, for the spine, and sometimes it's more of a mixed nerve. You can look at the functional tip of this muscle, but there's no such equivalent for the knee.

Sheila Rege: Any more discussion? I'd be interested in... does anybody here feel the easy thing, which is the foot and the shoulder? Do people think for the discussions, we should separate them? Is that the feeling I'm getting from the sentiment? Any more thoughts on discussion, safety, efficacy, cost. We've kind of gone through discussion on that, but any more according to people.

Kevin Walsh: I want to go back to a statement that I heard a couple people make, which was, if there was a better therapy, then I would opt for that, but there's not. So, I'll do this, because I have it. As someone who uses... as someone who has to prescribe Suboxone a lot because of opioid disorder in the community I live in and practice in, I feel like the same thesis has been applied to a lot of different kind of pain and led providers to use opioids chronically. So, I'm more and more of the school that says don't just do something, sit there, because the something that we're doing, too often, has unintended consequences that we only learn about later. So, I just don't accept the approach that says, gosh, if I had something better I would use it, but I don't. So, I have to do something, so I'll do this.

Mika Sinanan: To be clear, and so I understand your point, if we were to offer treatment that is an opioid-sparing approach, that in fact was effective. Let's assume that it is... I understand the evidence is limited, wouldn't that be an improvement over the default, which is opioids?

Kevin Walsh: Doing nothing is also an opioid-sparing approach.

Sheila Rege: We also heard that opioids don't work more than non-steroidals.

Mika Sinanan: They may not relieve the pain, but a lot of people end up on them, which is a different question.

Sheila Rege: I do have a question for our evidence... our expert mentioned hip. Did any of the studies ... that wasn't something I heard during the presentation. Was that looked at, at all, in any of the studies?

Valerie King: No. We looked... that wasn't part of our... we looked far and wide, and there were just no randomized trials of the hip at all. There is one in process.

Sheila Rege: Okay. What I'd like to do is maybe start with a straw poll on the easy. We can lump shoulder, foot, and hip if that's okay with people and do a straw poll on our questions and see where we, how we feel about it, get that taken care of, and then start a discussion again.

Josh Morse: Before we get too far into the straw poll, for the newbies, can you tell me what...

Sheila Rege: If we say... we'll start with the order it is here. In terms of safety with any of the ablation procedures, lumping all of them together, and we just gotta do shoulder, foot, or hip. Was there any evidence presented... and so if you say that it is safer than placebo in some, is it equivalent to placebo. I have no idea what more and all, how that would apply. Somebody will help me.

Gregory Brown: Well, it's better in every... every case, you know?

Sheila Rege: Less safe, or it's unproven. We just didn't hear anything. So, that... those are the cards.

Gregory Brown: So, it... actually when you frame the question, we need to put the comparator in there. I think that's what you're asking for.

Seth Schwartz: We used to only have more. So, is this intervention more effective than the comparators and the way the question was phrased to us was, if it's more under any potential circumstance, then you would vote more, and that seemed not granular enough? So, we split it to say more in some

versus more in all situations. That would be a stronger indication of positive evidence.

Sheila Rege: So, if I can kind of read what this book has, evidence based on safety is, now where that is. I saw it somewhere else, and now I can't find it.

Gregory Brown: Page 5?

Sheila Rege: No. The degree of harm associated with the risk. So, just... I look at it as placebo or whatever else.

Gregory Brown: Actually, I think in this case, it's important to say what are the usual treatments for knee arthritis? So, to me, when I'm looking at safety issues, I'm comparing it to NSAIDs and corticosteroid injections.

Sheila Rege: Okay. So, let's look at it then...

Gregory Brown: So, in terms of safety...

Sheila Rege: ...not to a knee replacement?

Gregory Brown: ...not to a knee, no, because this is a non-operative treatment. So, compared to NSAIDs and corticosteroid injections, is this more safe, equivalent, less safe, unproven.

Sheila Rege: So, here's where I found it. The evidence of the effect of using this technology on significant morbidity on health, but unlikely the result of long-lasting harm or life threatening, adverse effects on health that could result in lasting harm, morbidity, longterm complications, adverse non-fatal outcome. So, as compared to NSAIDs. Do we think for shoulder, foot, and hip, is this safer or is this... yeah. Let's say is it safer than NSAIDs?

Mika Sinanan: Sheila, are you asking us, just to be clear, on the basis of our...

Sheila Rege: Of the evidence.

Mika Sinanan: ...the data that was presented, the evidence?

Sheila Rege: The evidence... so, and I'm subdividing this to shoulder, foot, and hip. So, is this safer than NSAIDs?

Josh Morse: Ten unproven.

Sheila Rege: And that's shoulder, foot, and hip.

Josh Morse: So, forgive me for not remembering. Is that the comparator that was used in the trials?

Sheila Rege: What was the comparison used in the trials? We'll ask our experts.

Josh Morse: I think the basis of these questions is not hypothetical, but based on what you saw in the information presented to you.

Gregory Brown: So, multiple comparators were used. There were shams, there were corticosteroid injections. There was acetaminophen, and there was diclofenac. So, there were NSAIDs. So, what I would propose is that we know that NSAIDs and corticosteroid injections are effective. So, compared against your effective comparators. That would be the strongest [crosstalk].

Valerie King: So, did the committee want to know what the rundown was for the knee?

Sheila Rege: 30 seconds or less. Sure.

Valerie King: Conventional radiofrequency, there was one trial of 60 people in in that compared to Tylenol, NSAID, and physical therapy. None of the other five did. For cooled radiofrequency, it was all against intraarticular steroids. For cryoneurolysis, it was a sham.

Sheila Rege: Okay. So, I'm going to rephrase that, and we'll take another vote. Shoulder, foot, and hip, safety as compared to NSAIDs or physical therapy or intraarticular steroids, or sham.

Josh Morse: Ten unproven.

Sheila Rege: So, the next again, shoulder, foot, and hip, do we want any discussion before we go onto efficacy, effectiveness outcomes. Again, shoulder, foot, and hip. Any discussion or can we go to a straw poll. This is, again, as compared to the NSAIDs, physical therapy, intraarticular steroids, or sham.

Josh Morse: Ten unproven.

Sheila Rege: Cost.

Josh Morse: Ten unproven.

Sheila Rege: I would propose we vote on coverage on shoulder, foot, and hip. Is that in order whether to cover? So, for the new people, it's cover with conditions,

cover, or not cover, and that's for shoulder, foot, and hip. Are we going to cover this technology?

Female: [inaudible]

Sheila Rege: Yeah, she... [crosstalk]

Gregory Brown: Nothing was found. There was no evidence found, but it was included. Yeah.

Josh Morse: Ten not cover.

Sheila Rege: I'm following your orders to make it clear. Now, I would like to continue discussion of the knee. Any more questions for our expert on... and we're going to have to go through the same kind of thing for knee.

Tony Yen: I have a question for our expert. Can you help us interpret the evidence that we're supposed to be reviewing in terms of, like, the evidence that's in front of us? Do you feel like this is... would you agree that this is low quality evidence or are you seeing something very different?

Brett Stacey: I don't think it's very low quality. It's not high quality. That's for sure, but these are not very large studies. For the most part, the largest study is the cooled radiofrequency trial. All procedural trials are going to be conducted, hopefully, by interested parties, or they won't do the procedure well. So, they have to be interested parties. So, finding dispassionate people to do it is challenging. There certainly are efforts afoot at finding funding that is not tied to industry that is always going to be industry tied for 90-something percent of the time. So, that applies universally across these kind of things. There could have been better efforts at describing randomization and how they're going to try to blind people, and there are a bunch of other things that could have been better. So, it makes the... I think they're low quality. I wouldn't necessarily call them very low quality, but they're not super, like, wow. These are the best interventional studies around.

Tony Yen: Okay.

Sheila Rege: Are there studies currently being conducted that are larger scale, more multi-institutional in progress right now?

Gregory Brown: How does that change our vote?

Sheila Rege: I'm just asking if that's [crosstalk].

Brett Stacey: So, I know there... if you look at ClinicalTrials.gov, there are studies listed, which looked to be larger. I also know that there are efforts involving alternative funding sources, such as the federal government to try to look at multi-institutional studies and where to look at knee osteoarthritis and how to place this. They are not funded yet, but there are proposals happening. So, I think those things... that means that they are many, many years away.

John Bramhall: So, you have faith in this technology for knee pain. The data are not high quality that we see. What is it that drives your faith, personally?

Brett Stacey: Well, there are a bunch of the excluded studies are also there. Right? They're used for safety outcomes, but not even looked at for outcomes. There are other studies out there, and I guess, clinical... seeing people clinically. I mean, I'm not a standard interventional pain physician. I was raised in the world of rehab doctors, and I believe in comprehensive treatment, and I don't earn a salary based upon how many people I poke with a needle or burn or cut. So, I'm a little different, and I think this is... for knees, I think it's a superior technique to other things I have to offer people that have tried more conservative things. I'm particularly in conjunction with further efforts of conservative care.

Valerie King: Just for the committee's information, on page 137 of the report in Appendix F, there are the trials registered at ClinicalTrials.gov.

Sheila Rege: Any more discussion now? We're on knee, and the evidence was not particularly strong. How do we want to proceed? With more discussion? I'm thinking about a straw poll on safety of knee? Yeah. Any... so, let's go to a straw poll on, again, safety of this procedure for knee, as compared to NSAIDs, physical therapy, intraarticular steroids, or sham. So, is this safer? Or no, how should we phrase it? Is it...

Gregory Brown: So, if it's safer, it's more in some or all. If it's more harmful, then it's...

Sheila Rege: So, if it's safer than the alternatives.

Josh Morse: Six unproven, two, three, four more in some.

Sheila Rege: The next one is harder. We're looking at efficacy, effectiveness, and outcomes and the criteria based on the evidence presented was on function, pain, osteoarthritis index, the knee score. We're going to take away the shoulder thing. I'm going to take away the ankle, and pain could

be visual or numerical. So, it would be function, pain was better than NSAIDs, physical therapy, intraarticular steroids, or sham. Interesting. I thought I'd be the only unproven.

Josh Morse: I see two unproven, three unproven, and that would be seven more in some.

Sheila Rege: And do we want to discuss that? Good? Okay. How about costs? We're looking at cost and cost-effectiveness compared to the cadre, you know, the NSAIDs, physical therapy, cooling, steroids, and sham.

Josh Morse: Nine unproven, one equivalent.

Sheila Rege: So, at this point, I'd like, just going around the table maybe, on if we... what do you feel? Should we be thinking about not covering, covering if you had to right now, covering with conditions? I don't think anybody here is going to say cover unconditionally. I don't sense that. So, where is everybody leaning? Just go on around the table, see if we were very far spread apart, and we can talk again. That's what you would be doing. Okay.

Tony Yen: I'd vote not cover.

Chris Hearne: Cover with conditions probably.

Laurie Mischley: Not cover.

Sheila Rege: I'd go not cover. I'm on chair. I can't have say.

Gregory Brown: Cover with conditions.

Male: Cover with conditions.

Male: Cover with conditions.

Sheila Rege: So, we have enough for an interesting covering with conditions. So, let's start talking about what did the evidence show that we would say cover with conditions. That's kinda going to be the discussion. Then, we could... we need to discuss that. So, open to input.

John Bramhall: So, I don't like the idea of this... in my own mind, as a firstline modality. So, I would be happy if we could construct conditions that made it clear that this is not a firstline attack. Then, if we were going to go that way, we'd have to sort of work out, well what was the conventional set of therapies that you had to fail in order to get this procedure. It's a little bit

of a recapitulation of this morning in a way. So, that's where I'm sitting. I don't want to approve this as a firstline therapy, which would be approving it. Right? I want it conditional upon other more conservative, less destructive modalities having been failed.

Seth Schwartz: I would feel some of that. I mean, we have the entry criteria for the studies, but it seems like however you define it exactly, but chronic osteoarthritic knee pain that has been unresponsive to non-destructive therapies...

John Bramhall: For a period of time, perhaps.

Seth Schwartz: ...yeah, and I don't know what that time would be. I mean, I think there's probably some entrance criteria and things like that, that we could look A to see, 'cuz I would agree. I think there's a lot of reservations about this. So, I think limiting it makes a lot of sense, and we should figure out, okay. How do we want to limit it, but I certainly think chronicity and failure of all of the options is what we want to look at, as the step towards surgery.

Kevin Walsh: Would you put in a degree of arthritis in that or, I mean...

Seth Schwartz: You mean, like, severity of pain, that sort of thing? I would defer. I don't know... I don't really know whether that's used clinically as a marker or... I don't think we saw subdivisions within the data set. I mean, unless we know what the entry criteria were. I mean, if the entry criteria had the severity of arthritis set at a minimum standard, then certainly, it would be above that standard, but I don't know what that was.

Gregory Brown: It was Kellgren-Lawrence grade 3 or 4. I mean, I don't think I've ever seen an x-ray that says no degenerative changes. So, I think you'd want to say Kellgren-Lawrence grade 3 or 4.

Seth Schwartz: Do we know what the entry criteria were for the main studies?

Sheila Rege: Yeah. What, what did the studies use?

Gregory Brown: It was variable.

Valerie King: So, not all of them gave a radiologic grade. The ones that did, it ranged from 2 to 3 to 4 on a Kellgren-Lawrence scale. I think it's also hard to parse from the studies that were available, were these people eligible for a knee replacement or an arthroplasty, or was there some reason that they were not. That's a little hard to figure out, as well.

Seth Schwartz: Was there information regarding just clinical severity of their arthritis, duration of symptoms, or any of those sorts of things, as far as entry criteria for those studies?

Valerie King: Yeah. Everything is in the study characteristics. So, starting on page 76 in table 4, it goes study by study. So, I would say in general, these are people who have years of duration, five, six, seven years of duration of pain, have quite high VAS scores, and whose knees are not... who are quite symptomatic, but many of the studies included, because radiologic grade does not always correlate very well, as those of you who do back stuff know especially, you can have not much radiologic change. So, a Kellgren-Lawrence 2 but quite severe pain. So, it's, there is not a good correlation there.

Gregory Brown: I would caution you about doing anything other than Kellgren-Lawrence grading, because you can have non-specific knee pain that's horrible and a normal knee x-ray, or the evidence is for knee arthritis, then they don't have knee arthritis, and their pain, we have no idea what the effect is going to be for a nerve ablation.

Seth Schwartz: Well, I would agree with that, that they clearly need... they clearly should have evidence that this is an osteoarthritic cause of pain. Now, I don't know the literature well enough to say this to indicate adequate to say that they have arthritis in their knee.

Gregory Brown: Like I said, for basically... to qualify for a knee replacement or the BREE criteria now, you need to have grade 3 and failed all treatments basically, or grade 4. Grade 4 is bone on bone. So, I think just to manage it, you want to say they have to have radiographic grade 3 or 4. You don't want to set up any old number, because, I mean, you get some people that, oh, it really just started bothering me the last couple weeks, but they've bone on bone for the last five years. Then, you've got other people that hardly have any narrowing, and they're saying my pain is 11 out of 10. So, I just... the most objective thing in everything I've ever seen, including the BREE criteria, uses Kellgren-Lawrence grading.

Seth Schwartz: So, the question that was... I think that's totally reasonable, but then we would be setting the standard even higher. In other words, should there also be some... well, maybe pain isn't the marker, but, I mean, is there some, you know, standardized criteria that we've looked at, as far as, like, a quality of life measure, or whatever those are. Just, is there some other standard of measure that indicates symptomatology from it, and we could also set it at a higher standard.

Gregory Brown: They didn't set any limit or number for a knee replacement. So, it wasn't, like, you needed to have a... they're actually using what's called [inaudible] Junior, but they didn't say you need a [inaudible] Junior score of this to qualify. I mean, the fact that they're presenting that they're, like, my function is diminished. My pain is there, I need knee surgery, but trying to find a number threshold, we didn't do it in BREE.

Seth Schwartz: Well, that's fine. Then we don't need to specify. We could simply say persistent pain that's not been responsive to, and we can classify what the other...

Brett Stacey: To document it. Can I comment?

Gregory Brown: Sure.

Brett Stacey: So, I think that's confusing to talk about knee replacement, as a comparison to a much less structurally oriented procedure. So, I understand for knee replacement, we are changing the structure while focusing on the degree of degradation of the knee joint is really important, but for patients with chronic pain, a significant portion of the folks in the cooled RF study were grade 2, and as Valerie said, there's not really any difference that they reported with the outcome between the grade 2 and grade 3 or grade 4 people. So, it's to treat pain. It's not to correct the structural problems. So, it's not a surgical intervention. So, I think they have to have some objective problem with the joint. I completely agree with that, but it doesn't have to be severe for them to have severe pain. We don't put those restrictions on other types of pain procedures often. It's not usually typically based upon...

Sheila Rege: But this is something that commercial insurances in our state are not covering that this committee is discussing potentially coverage with conditions for Medicaid ahead of commercial.

Male: [inaudible]

Sheila Rege: Mm-hmm. So, be aware, when you're creating criteria, because knee pain, a lot of my patients have it. I mean, we have knee pain. I would like people who said it was unproven to speak. Do you want to change anybody's mind? This is the discussion while we're trying to figure out where we're going with this.

Janna Friedly: I can start. As I mentioned, I'm very much on the fence, but I think the combination of things, including this discussion about who is eligible and what criteria we use, which we don't have enough data to really

understand that. I don't have enough longterm outcome data or safety data. Then, just looking through the trials that are coming up, there are a number of trials that are going to be published, that are, you know, that are completed, as of, like, this month or last month, that look like they are larger studies that may answer some of these questions. So, I feel like we're on the cusp of having an answer, but we don't have the answer yet. So, for me, I just... to come up with criteria for who should get this procedure, how many you should cover. Is it a onetime procedure? Do you do this repeatedly, how often? I don't have any answers to any of those to start crafting criteria. For me, it would be very difficult in the absence of the right evidence.

Austin McMillin: And I also didn't see the evidence that really convinced me that this should be something that's covered based on that, but the compassionate side of me in trying to get people some relief, and the common sense side says that it's good to do something, but then you also have the arguments that, you know, sometimes what we're getting into, we really don't know longterm what's happening. I hesitate to use pain as a guide, because I've got patients that come in all the time and score themselves at a ten on a zero to ten. So, even that, to me, is unreliable on face value when I'm watching their behavior. I think there has to be something more than just even a pain score to be able to drive a procedure like this. Even in terms of taking a look at what happens in the spine, which is not what we're dealing with here, there's good research out that shows that you do radiofrequency ablation just fine, and that's the level that would be degenerative in two years, and you have to rig a motor component to that, but there's also propriosensory function to that. So, I'm a little bit disturbed about that, in terms of what we're actually doing. What we're willing to do to drop the pain down and now knowing what else has been done for the patient, including cognitive behavioral therapy or whatever else, meditation, things that they may be able to do to help self-manage pain. I really don't know, but we're dealing with a procedure and then a group. So, I'm trying to put all of that into all of that context, and then taking a look at the research, which really isn't strong for me. It left me with lots of questions and small end numbers and short follow-ups and bias, and it made me a little bit uncomfortable to be able to use that literature to then open the door to coverage. Then, we're now having to struggle to try and figure out how we put some parameters around that. So, I'm still in the unproven category for that, for those reasons.

Sheila Rege: I think short of our expert saying it works in the real world, the data didn't leave me with a warm, fuzzy feeling. The compassionate side is, it seems to work in the real world, but then I'm wrestling with, you know, a lot of

the other commercial insurance companies are not covering it. There are studies in the pipeline. I mean, do we want to be the trailblazers?

Austin McMillin: And I personally don't have a problem with that. I think that commercial insurance doesn't want to cover most anything. So, I don't have any problem being a trailblazer, but I really need something to be able to drive me there so I feel comfortable about the fact that we're actually doing that for these reasons and the data, at least what was presented from the vendor, just didn't get me there.

Gregory Brown: I echo Mika's comment at the end, and I think that applying a rigid set of grade criteria and downgrading every single study three or four levels, but not applying that same criteria to the evidence for NSAIDs, the evidence for corticosteroids, the evidence for hyaluronic acid, the evidence for other treatments that are currently being used, and some very expensive, paints an unfair picture of the evidence in this situation.

Austin McMillin: Well, what I would argue that not having evidence about the comparators leaves me further in question about the results of the study, and I know that there's a lot of... there are a lot of treatments that are being used that just don't have the evidence, but we're here to talk about the evidence about ablation. So, those are just to me shortcomings in the studies.

Gregory Brown: That's why what's compelling to me is I did the network meta-analysis that recorded the effectiveness of non-operative treatments. Number one effective treatment for pain and function is naproxen. Number one effective treatment for function is naproxen. Number one treatment for pain is corticosteroid, and in the trials they compare with corticosteroids and compare with non-steroidals. This was better than both.

Sheila Rege: So, I'm going to go through a straw poll right now, and I just want a yes/no. Raise your hands if we should continue... if we want to continue to now start crafting... are we comfortable enough that we want to start crafting language. So, who in this group feels the evidence was good enough that we want to try and craft language that we would then vote up or down, as a decision? One, two, three, four.

Gregory Brown: Well, then there's no point in drafting if there are six that are going to vote for non-cover.

Sheila Rege: Well, we've never had it this close before. Oh, we have been here before?

Austin McMillin: Just because we're kind of on the fence with some changed votes. How would we go about crafting parameters, you know, conditions, up on the screen?

Mika Sinanan: Can I make some suggestions in that regard? We're talking about a knee. We're talking about a single treatment. We're talking about documented arthritis by radiologic score. We have to set the parameters for that. So, that requires at least one x-ray and a level of damage. We're talking about the presence of chronic pain for a period of time that has failed conventional treatment, including, we can list them that are available to that patient. Some are not going to be available, because of comorbidities, but some will be. Then, at the end of that, I would propose that we put into place a plan for a one or two year review, because that's when the new data comes out. That would be kind of a way to think about this. Then, we're setting... we're making it available, but under some pretty strict criteria, as long as the agency feels that those are interpretable data, interpretable basis, and we would plan to come back and look at the data in two years. That would be my proposal.

Sheila Rege: Does the agency know how many denials you have had for this procedure? Have there been requests and denials? We don't have a number? Well, Mika has a motion on the floor, so to speak. I suspect a second.

Gregory Brown: Sure.

Sheila Rege: Do we want to vote it up or down? Do we want to continue or not? Right now, I think it was six to four. By the way, it's quarter to 4:00, and we're going to be here until we finish this, and I wanted my first meeting to be very efficient, and it's not going well. So, comments.

Seth Schwartz: I was just going to say, I think at this stage, if you want, we can go ahead and vote. Then, if it turns out that it's either split or cover with conditions is favored, then we can develop those conditions further.

Sheila Rege: Let's do that. I've been touchy feely about making sure. So, your vote on the pink, the real ones.

Austin McMillin: Are we talking about the covered with conditions with the motion that's on the floor?

Sheila Rege: Or not cover.

Austin McMillin: Or not at all. It's a vote between those two things?

Josh Morse: Oh, you're not going to fluster it up further?

Sheila Rege: No, we're not, because if it gets voted down, if six...

Gregory Brown: Not if six out of four...

Sheila Rege: ...vote it down...

Gregory Brown: ...are going to vote not cover.

Sheila Rege: ...then it's done. We're done.

Josh Morse: Okay. Did we type those up?

Sheila Rege: Don't worry. We won't have to. We will if it goes.

Gregory Brown: If it's five to five, we'll put something up there, or [crosstalk].

Sheila Rege: If it's five to five we'll put something up, but if...

Josh Morse: You are the chair. Six not cover, four cover with conditions. Okay. So, we need to look at national coverage determination and guidelines, please.

Sheila Rege: Is everybody okay? I mean, with that? I mean, I don't like it when it's close, especially when Dr. Sinanan has something... some words of wisdom. So, now going on to... so, now we don't have to do the costs and stuff at this point. So, let's look at the national coverage. There wasn't any national guidelines that I saw.

Josh Morse: Right. So, for the new committee members, on page seven, it talks about discussion at the middle of the table, right near the middle of the binder here, is the determination consistent with identified Medicare decisions and expert guidelines, and Medicare decisions, by definition are, in this case, are the national coverage determinations, so not local coverage determinations but from a national, and then expert guidelines. Then, if your determination is not consistent, we ask that you explain for the record why not and what evidence you relied upon that resulted in a difference, whether it's Medicare or guidelines. That's why I asked those questions.

Gregory Brown: I'm sorry.

Sheila Rege: So, there was no national coverage. So, I think we're...

Josh Morse: So, that one's covered.

Sheila Rege: ...that one's covered.

Gregory Brown: And there's no clinical practice guidelines.

Sheila Rege: I'm sure, there's none. Okay. Do we have, as a committee, what I heard was that there may be new data. Do we, as a committee, can we ask that this come back before us at a certain period of time?

Gregory Brown: Anybody can make that request when new evidence comes up.

Kevin Walsh: I would trust that the vendors will make that request.

Sheila Rege: Okay. So, we don't have to? Okay.

Josh Morse: And the program does monitor for new literature, and certainly we encourage anybody to let us know if there's new literature. Then, we bring that to you.

Sheila Rege: Any other discussion? Any other items, or will be adjourned?

Gary Franklin: Can I ask a question? I'm sorry. So, the decision is not to cover this nerve ablation for any chronic pain, because you talked about the knee, you talked about the other three, which, you know, the evidence was weak, but we also get requests for all manner of other kinds of nerve in the limb. It's not just those four things. So, I'm presuming that because there was no evidence on the other things, then the non-coverage decision includes all chronic pain of the limb.

Kevin Walsh: We were only presented evidence for the knee, the shoulder, and the foot. How can we make a decision about anything else?

Gary Franklin: Well, because there was no evidence on the other things. There's nothing.

Valerie King: In so, was anything in the limb. So, we looked for elbows, wrists, fingers, toes, hips, there's nothing.

Sheila Rege: So, if this committee... so, to confirm this, are we comfortable with the agency medical director statement, peripheral nerve ablation is not a covered benefit for the treatment of chronic limb pain?

Austin McMillin: I'm sorry. Can I ask, did that include the amputation of phantom limb phenomenon or, in the research?

Valerie King: There is a trial registered on phantom limb pain, but there aren't any currently available ones.

Sheila Rege: So, just a raise of hands for a vote that everybody is in agreement, because I did parse it out, peripheral nerve ablation is not a covered benefit for the treatment of chronic limb pain. Do we still have those six or did somebody change their mind?

Mika Sinanan: We've agreed that we're not covering anything. So, we're not covering anything.

Sheila Rege: So, everybody... so, you're good with that. We don't have to.

Josh Morse: When I think about this, I look at the scoping documents, which we normally try to have that right next to this for reference. That is how the scope was written. So, that's what evidence was sought by Dr. King, and that's what your policy applies to.

Gregory Brown: Okay.

Josh Morse: Thank you.

Gregory Brown: Thank you all.

Mika Sinanan: Just for clarification, we're waiting for somebody to request a rereview or can we ourselves request a rereview in a couple years when the [crosstalk].

Gregory Brown: I mean, if there's new evidence.

Mika Sinanan: If there's new, well, but there are all these RCT's that are...

Gregory Brown: Right. Exactly.

Mika Sinanan: ...oh, I'm sorry.

Gregory Brown: But again, yeah. So, anybody can request it.

Josh Morse: We actively look with the existing...

Mika Sinanan: [crosstalk] documentation of the purposes, we're not saying never. What we're saying is we're waiting for the data, and we are looking forward to a rereview on the basis of the new data.

Josh Morse: Thank you.